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Dated 6 January 2004

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Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your reference — 100859

2. Patent application number *(The Patent Office will fill in this part)* — 0227701.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* — 7822448003

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

Dr Anne Williams

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)* — 8470877001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

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Continuation sheets of this form	
Description	58 ✓
Claim(s)	10 ✓
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date

Authorised Signatory 27/11/2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

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CHEMICAL COMPOUNDS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing substituted oxazolidinone and/or isoxazoline rings. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

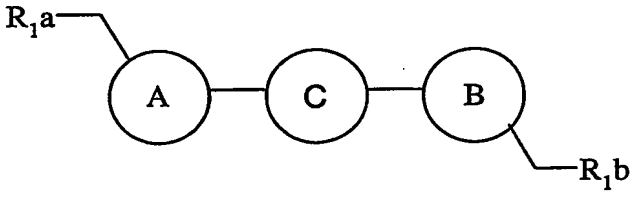
The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including H.influenzae and M.catarrhalis.

Certain antibacterial compounds containing an oxazolidinone ring have been described in the art (for example, Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and 1989, 32(8), 1673-81; Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165). Bacterial resistance to known antibacterial agents may develop, for example, by (i) the evolution of active binding sites in the bacteria rendering a previously active pharmacophore less effective

or redundant, and/or (ii) the evolution of means to chemically deactivate a given pharmacophore, and/or (iii) the evolution of efflux pathways. Therefore, there remains an ongoing need to find new antibacterial agents with a favourable pharmacological profile, in particular for compounds containing new, more potent, pharmacophores.

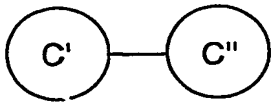
We have discovered a class of bi-aryl antibiotic compounds containing two substituted oxazolidinone and/or isoxazoline rings which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and/or linezolid and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams, but also to fastidious Gram negative strains such as H.influenzae, M.catarrhalis, mycoplasma spp. and chlamydial strains. The compounds of the invention contain two groups capable of acting as pharmacophores. The two groups may independently bind at pharmacophore binding sites where the sites may be similar or different, where the similar or different sites may be occupied simultaneously or not simultaneously within a single organism, or where the relative importance of different binding modes to the similar or different sites may vary between two organisms of different genus. Alternatively one of the groups may bind at a pharmacophore binding site whilst the other group fulfills a different role in the mechanism of action.

Accordingly the present invention provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

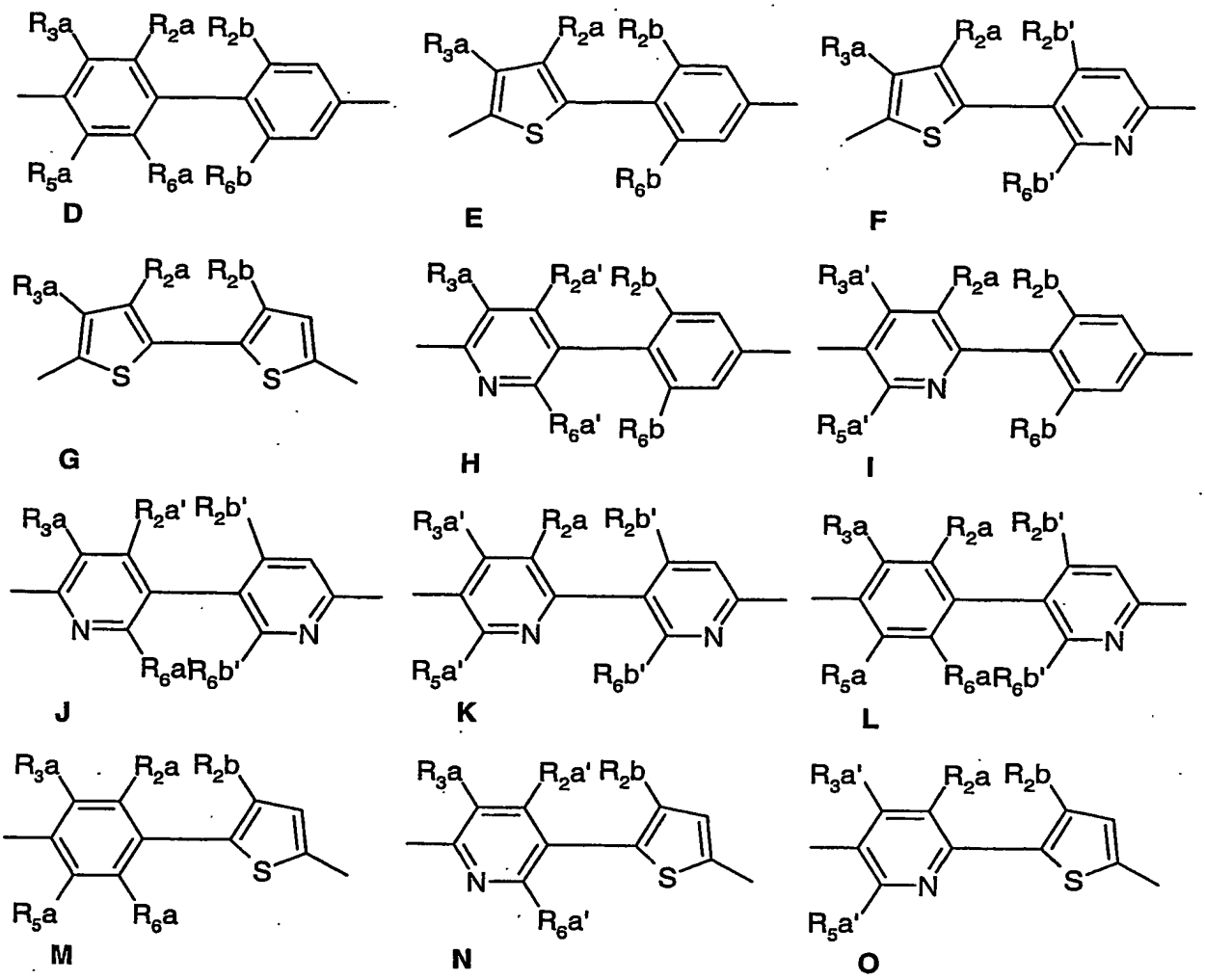


(I)

wherein in (I) C is a biaryl group C'-C''



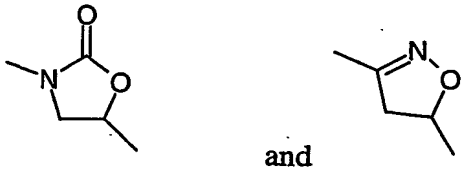
where C' and C'' are independently aryl or heteroaryl rings such that the group C is represented by any one of the groups D to O below:



wherein the groups D to O are attached to rings A and B orientation [(A-C') and (C''-B)] shown and

wherein A and B are independently selected from

i) ii)



and

wherein i) and/or ii) are linked as shown in (I) via the 3-position to group C and substituted in the 5-position as shown in (I) by $-CH_2-R_1a$ and $-CH_2-R_1b$;

R_2b and R_6b are independently selected from H, F, Cl, OMe, Me, Et and CF_3;

R_2b' and R_6b' are independently selected from H, OMe, Me, Et and CF_3;

R_2a and R_6a are independently selected from H, Br; F, Cl, OMe, SMe; Me, Et and CF_3;

R_2a' and R_6a' are independently selected from H, OMe, SMe; Me, Et and CF_3;

R_3a and R_5a are independently selected from H, (1-4C)alkyl, Br, F, Cl, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2), amino, (1-4C)alkylcarbonylamino, nitro, cyano, -CHO, -CO(1-4C) alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

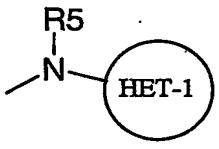
R_3a', R_5a' are independently selected from H, (1-4C)alkyl, OH, (1-4C)alkoxy, (1-4C)alkylthio, amino, (1-4C)alkylcarbonylamino, nitro, cyano, -CHO, -CO(1-4C)alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

wherein any (1-4C)alkyl group may be optionally substituted with F, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2) or cyano;

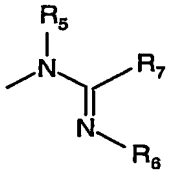
wherein at least one of R_2a, R_6a R_2a', R_6a' R_3a, R_5a, R_3a', R_5a' is not H;

wherein when ring C' is a pyridine ring (ie when group C is group H, I, J, K, N or O) the ring nitrogen may optionally be oxidised to an N-oxide;

R_1a and R_1b are independently selected from hydroxy, -OSi(tri-(1-6C)alkyl) (wherein the 3 (1-6C)alkyl groups are independently selected from all possible (1-6C)alkyl groups), $-NR_5C(=W)R_4$, $-OC(=O)R_4$,

a) 

, b) 

and c) 

wherein W is O or S;

R_4 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, (1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)$p(3-6C)cycloalkyl or $-(CH_2)$p(3-6C)cycloalkenyl wherein p is 0, 1 or 2; and wherein at each occurrence, alkyl, alkenyl, cycloalkyl cycloalkenyl in substituents in R_4 is optionally substituted with one, two, three or more F, Cl or CN;

R_5 is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl), $-CO_2R_8$, $-C(=O)R_8$, $-C(=O)SR_8$, $-C(=S)R_8$, $P(O)(OR_9)(OR_{10})$ and $-SO_2R_{11}$, wherein R_8, R_9, R_{10} and R_{11} are as defined hereinbelow;

HET-1 is selected from HET-1A and HET-1B wherein:

HET-1A is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms

independently selected from N, O and S; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one or two substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-1B is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one, two or three substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2 is selected from HET-2A and HET-2B wherein

HET- 2A is an N-linked 5-membered, fully or partially unsaturated heterocyclic ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom, other than a C atom adjacent to the linking N atom, by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by a substituent selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2B is an N-linked 6-membered di-hydro-heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom, other than a C atom adjacent to the linking N atom, by oxo or thioxo and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by one or two substituents independently selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

RT is selected from a substituent from the group:

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro; or

(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino, and (2-4C)alkenylamino;

or RT is selected from the group

(RTb1) (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or

(RTb2) (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl,and (3-6C)cycloalkenyl;

or RT is selected from the group

(RTc) a fully saturated 4-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or carbon atom;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), (RTb1) or (RTb2), or (RTc) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;

R_6 is cyano, $-COR_{12}$, $-COOR_{12}$, $-CONHR_{12}$, $-CON(R_{12})(R_{13})$, $-SO_2R_{12}$, $-SO_2NHR_{12}$, $-SO_2N(R_{12})(R_{13})$ or NO_2, wherein R_{12} and R_{13} are as defined hereinbelow;

R_7 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, (1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl or $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_8 is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy, cyano, up to 3 halogen atoms and $-NR_{15}R_{16}$ (wherein R_{15} and R_{16} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{15})(R_{16})$ group, R_{15} and R_{16} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring);

R_9 and R_{10} are independently selected from hydrogen and (1-4C)alkyl;

R_{11} is (1-4C)alkyl or phenyl;

R_{12} and R_{13} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{12})(R_{13})$ group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring which ring may be optionally substituted by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl.

In this specification, HET-1A and HET-1B are fully unsaturated ring systems.

In this specification, HET-2A may be a fully or partially unsaturated heterocyclic ring, provided there is some degree of unsaturation in the ring.

Particular examples of 5-membered heteroaryl rings containing 2 to 4 heteroatoms independently selected from N, O and S (with no O-O, O-S or S-S bonds) are pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, isothiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,2,3-thiadiazole.

Particular examples of 6-membered heteroaryl ring systems containing up to three nitrogen heteroatoms are pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine.

Particular examples of N-linked 5-membered, fully or partially unsaturated heterocyclic rings, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom include, for example, pyrazole, imidazole, 1,2,3-triazole (preferably 1,2,3-triazol-1-yl), 1,2,4-triazole (preferably 1,2,4-triazol-1-yl) and tetrazole (preferably tetrazol-2-yl) and furazan.

Particular examples of N-linked 6-membered di-hydro-heteroaryl rings containing up to three nitrogen heteroatoms in total (including the linking heteroatom) include di-hydro versions of pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine and pyridine.

Particular examples of halogen-substituted alkyl substituents in HET-1 and HET-2 are monofluoromethyl, difluoromethyl and trifluoromethyl.

A particular example of R_8 as a halogen-substituted alkyl group is trifluoromethyl.

In this specification the term 'alkyl' includes straight chain and branched structures. For example, (1-4C)alkyl includes propyl and isopropyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chain version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. A similar convention applies to other radicals, for example halo(1-4C)alkyl includes 1-bromoethyl and 2-bromoethyl.

In this specification, the terms 'alkenyl' and 'cycloalkenyl' include all positional and geometrical isomers.

In this specification, the term 'aryl' is an unsubstituted carbocyclic aromatic group, in

particular phenyl, 1- and 2-naphthyl.

For the avoidance of doubt, reference to a carbon atom in HET1 or HET2 being substituted by an oxo or thioxo group means replacement of a CH2 by C=O or C=S respectively.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

Examples of **(1-4C)alkyl** and **(1-5C)alkyl** include methyl, ethyl, propyl, isopropyl and t-butyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, t-butyl, pentyl and hexyl; examples of **(1-10C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl and nonyl; examples of **(1-4C)alkanoylamino-(1-4C)alkyl** include formamidomethyl, acetamidomethyl and acetamidoethyl; examples of **hydroxy(1-4C)alkyl** and **hydroxy(1-6C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **2-((1-4C)alkoxycarbonyl)ethenyl** include 2-(methoxycarbonyl)ethenyl and 2-(ethoxycarbonyl)ethenyl; examples of **2-cyano-2-((1-4C)alkyl)ethenyl** include 2-cyano-2-methylethenyl and 2-cyano-2-ethylethenyl; examples of **2-nitro-2-((1-4C)alkyl)ethenyl** include 2-nitro-2-methylethenyl and 2-nitro-2-ethylethenyl; examples of **2-((1-4C)alkylaminocarbonyl)ethenyl** include 2-(methylaminocarbonyl)ethenyl and 2-(ethylaminocarbonyl)ethenyl; examples of **(2-4C)alkenyl** include allyl and vinyl; examples of **(2-4C)alkynyl** include ethynyl and 2-propynyl; examples of **(1-4C)alkanoyl** include formyl, acetyl and propionyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-6C)alkoxy** and **(1-10C)alkoxy** include methoxy, ethoxy, propoxy and pentoxy; examples of **(1-4C)alkylthio** include methylthio and ethylthio; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-4C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and dipropylamino; examples of **halo** groups include fluoro, chloro and bromo; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl and ethylsulfonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxy** and **(1-6C)alkoxy-(1-6C)alkoxy** include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of **(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy** include 2-(methoxymethoxy)ethoxy,

2-(2-methoxyethoxy)ethoxy; 3-(2-methoxyethoxy)propoxy and 2-(2-ethoxyethoxy)ethoxy; examples of **(1-4C)alkylS(O)$_2$amino** include methylsulfonylamino and ethylsulfonylamino; examples of **(1-4C)alkanoylamino** and **(1-6C)alkanoylamino** include formamido, acetamido and propionylamino; examples of **(1-4C)alkoxycarbonylamino** include methoxycarbonylamino and ethoxycarbonylamino; examples of **N-(1-4C)alkyl-N-(1-6C)alkanoylamino** include N-methylacetamido, N-ethylacetamido and N-methylpropionamido; examples of **(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include methylsulfinylamino, methylsulfonylamino, ethylsulfinylamino and ethylsulfonylamino; examples of **(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-** wherein p is 1 or 2 include methylsulfinylmethylamino, methylsulfonylmethylamino, 2-(ethylsulfinyl)ethylamino and 2-(ethylsulfonyl)ethylamino; examples of **fluoro(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include trifluoromethylsulfinylamino and trifluoromethylsulfonylamino; examples of **fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)NH-** wherein p is 1 or 2 include trifluoromethylsulfinylmethylamino and trifluoromethylsulfonylmethylamino examples of **(1-4C)alkoxy(hydroxy)phosphoryl** include methoxy(hydroxy)phosphoryl and ethoxy(hydroxy)phosphoryl; examples of **di-(1-4C)alkoxyphosphoryl** include di-methoxyphosphoryl, di-ethoxyphosphoryl and ethoxy(methoxy)phosphoryl; examples of **(1-4C)alkylS(O)$_q$-** wherein q is 0, 1 or 2 include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of **phenylS(O)$_q$** and **naphthylS(O)$_q$-** wherein q is 0, 1 or 2 are phenylthio, phenylsulfinyl, phenylsulfonyl and naphthylthio, naphthylsulfinyl and naphthylsulfonyl respectively; examples of **benzyloxy-(1-4C)alkyl** include benzyloxymethyl and benzyloxyethyl; examples of a **(3-4C)alkylene** chain are trimethylene or tetramethylene; examples of **(1-6C)alkoxy-(1-6C)alkyl** include methoxymethyl, ethoxymethyl and 2-methoxyethyl; examples of **hydroxy-(2-6C)alkoxy** include 2-hydroxyethoxy and 3-hydroxypropoxy; examples of **(1-4C)alkylamino-(2-6C)alkoxy** include 2-methylaminoethoxy and 2-ethylaminoethoxy; examples of **di-(1-4C)alkylamino-(2-6C)alkoxy** include 2-dimethylaminoethoxy and 2-diethylaminoethoxy;

examples of **phenyl(1-4C)alkyl** include benzyl and phenethyl; examples of **(1-4C)alkylcarbamoyl** include methylcarbamoyl and ethylcarbamoyl; examples of **di((1-4C)alkyl)carbamoyl** include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of **hydroxyimino(1-4C)alkyl** include hydroxyiminomethyl, 2-(hydroxyimino)ethyl and 1-(hydroxyimino)ethyl; examples of **(1-4C)alkoxyimino-(1-4C)alkyl** include

methoxyiminomethyl, ethoxyiminomethyl, 1-(methoxyimino)ethyl and 2-(methoxyimino)ethyl; examples of **halo(1-4C)alkyl** include, halomethyl, 1-haloethyl, 2-haloethyl, and 3-halopropyl; examples of **nitro(1-4C)alkyl** include nitromethyl, 1-nitroethyl, 2-nitroethyl and 3-nitropropyl; examples of **amino(1-4C)alkyl** include aminomethyl, 1-aminoethyl, 2-aminoethyl and 3-aminopropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl; examples of **(1-4C)alkanesulfonamido** include methanesulfonamido and ethanesulfonamido; examples of **(1-4C)alkylaminosulfonyl** include methylaminosulfonyl and ethylaminosulfonyl; examples of **di-(1-4C)alkylaminosulfonyl** include dimethylaminosulfonyl, diethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl; examples of **(1-4C)alkanesulfonyloxy** include methylsulfonyloxy, ethylsulfonyloxy and propylsulfonyloxy; examples of **(1-4C)alkanoyloxy** include acetoxy; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl and ethylaminocarbonyl; examples of **di((1-4C)alkyl)aminocarbonyl** include dimethylaminocarbonyl and diethylaminocarbonyl; examples of **(3-8C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(4-7C)cycloalkyl** include cyclobutyl, cyclopentyl and cyclohexyl; examples of **di(N-(1-4C)alkyl)aminomethylimino** include dimethylaminomethylimino and diethylaminomethylimino.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or

substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

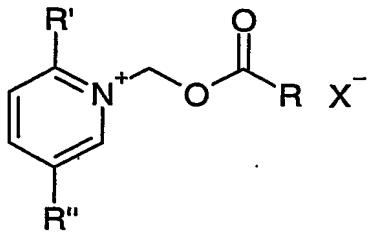
d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent alcohol.

Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

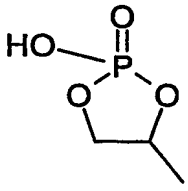
Suitable pro-drugs for pyridine derivatives include acyloxymethyl pyridinium salts eg halides; for example a pro-drug such as:



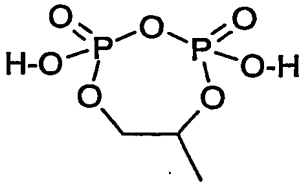
An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as

phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl, carboxy(2-5C)alkylcarbonyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include chloromethyl or aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example, $R^A C(O)O(1\text{-}6C)alkyl\text{-}CO$- (wherein R^A is for example, optionally substituted benzyloxy-(1-4C)alkyl, or optionally substituted phenyl; suitable substituents on a phenyl group in such esters include, for example, 4-(1-4C)piperazino-(1-4C)alkyl, piperazino-(1-4C)alkyl and morpholino-(1-4C)alkyl.

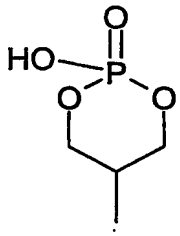
Suitable in-vivo hydrolysable esters of a compound of the formula (I) are described as follows. For example, a 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a pyrophosphate of formula (PD2), and a 1,3-diol may be cyclised to form a cyclic ester of the formula (PD3):



(PD1)



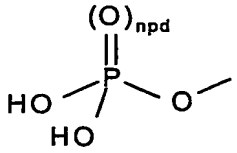
(PD2)



(PD3)

Esters of compounds of formula (I) wherein the HO- function/s in (PD1), (PD2) and (PD3) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of invention in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD4) :



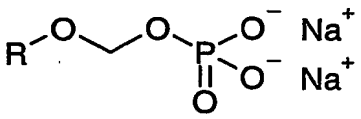
(PD4)

For the avoidance of doubt, phosphono is $-P(O)(OH)_2$; (1-4C)alkoxy(hydroxy)-phosphoryl is a mono-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$; and di-(1-4C)alkoxyphosphoryl is a di-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$.

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD4) in which either or both of the -OH groups in (PD4) is independently protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2), (PD3) and (PD4) may be prepared by reaction of a compound of invention containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

Other suitable prodrugs include phosphonooxymethyl ethers and their salts, for example a prodrug of R-OH such as:

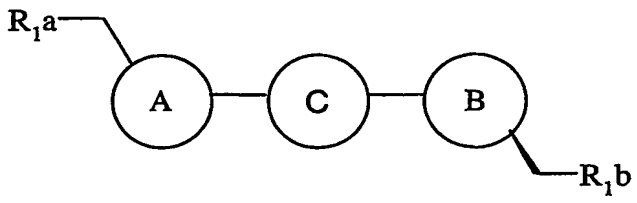


When a compound of invention contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2), (PD3) and/or (PD4) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo hydrolysable ester prodrug of a compound of invention contains two (PD4) groups, there are four HO-P- functionalities present in the overall molecule, each of which may form

an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

The compounds of the present invention have a chiral centre at both of the C-5 positions of the oxazolidinone and/or isoxazoline rings. The pharmaceutically active diastereomers are of the formula (IA):



(IA)

wherein the chiral centre of ring B is fixed in the orientation shown (generally the (5R) configuration, depending on the nature of R_1b, C and B) and ring B is acting as a pharmacophoric group; and wherein the orientation of the chiral centre at ring A may vary and may influence whether ring A also independently binds to a pharmacophore binding site.

The present invention includes pure diastereomers or mixtures of diastereomers, for example a racemic mixture. If a mixture of enantiomers is used, a larger amount (depending upon the ratio of the enantiomers) will be required to achieve the same effect as the same weight of the pharmaceutically active enantiomer.

Furthermore, some compounds of the invention may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereoisomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity as described hereinafter.

The invention relates to all tautomeric forms of the compounds of the invention that possess antibacterial activity.

It is also to be understood that certain compounds of the invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial

activity.

It is also to be understood that certain compounds of the invention may exhibit polymorphism, and that the invention encompasses all such forms which possess antibacterial activity.

As stated before, we have discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics, together with activity against fastidious Gram negative pathogens such as H.influenzae, M.catarrhalis, Mycoplasma and Chlamydia strains. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

In one embodiment of the invention are provided compounds of formula (I), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

In one aspect, an in-vivo hydrolysable ester of a compound of the formula (I) is a phosphoryl ester (as defined by formula (PD4) with npd as 1).

Compounds of the formula (I), or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein C is selected from any one of groups D to O represent separate and independent aspects of the invention.

Particularly preferred compounds of the invention comprise a compound of the invention, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein the substituents A, B, R_1a, R_1b, R_2a, R_2b, R_3a, R_3b R_5a, R_5a', R_6a and $R_6a'$and other substituents mentioned above have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

In one embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group D.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group E.

In another embodiment are provided compounds as defined herein in formula (I) or a

pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group H.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group I.

In another embodiment are provided compounds of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which the group C is a group selected from D, E, H and I as hereinbefore defined.

In a further embodiment are provided compounds of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which the group C is a group selected from D and E as hereinbefore defined.

In a further embodiment are provided compounds of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which the group C is a group selected from D and H as hereinbefore defined.

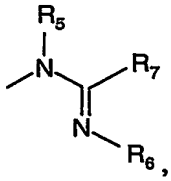
In one aspect both A and B are oxazolidinone rings.

In another aspect, either A or B is an oxazolidinone ring and the other is an isoxazoline ring.

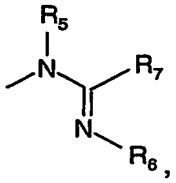
In a further aspect, both A and B are isoxazoline rings.

In one aspect, R_2b and R_6b are independently H or F.

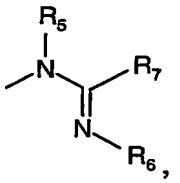
In one aspect R_2b' and R_6b' are both H.

In one embodiment, R_1a and R_1b are independently selected from hydroxy, -NHC(=W)R_4, -OC(=O)R_4, and  , wherein W, R_5 and R_6 are as defined hereinbefore, R_4 is selected from hydrogen, amino, (1-4C)alkyl, -NH(1-4C)alkyl, -N(di-(1-4C)alkyl), -O(1-4C)alkyl, -S(1-4C)alkyl, (2-4C)alkenyl, -(CH_2)p(3-6C)cycloalkyl and -(CH_2)p(3-6C)cycloalkenyl wherein p is 0, 1 or 2; and R_7 is selected from hydrogen, (1-8C)alkyl, -OR_{12}, -SR_{12}, amino, NHR_{12}, $N(R_{12})(R_{13})$, (1-8C)alkylaryl and mono-, di-, tri- and per-halo(1-8C)alkyl.

In another embodiment, R_1a and R_1b are independently selected from hydroxy,

-NHC(=W)R_4, -OC(=O)R_4, and  ,

wherein W, R_4, R_5, R_6 and R_7 are as defined hereinbefore, especially wherein R_4 is (1-4C)alkyl, (1-4C)alkoxy, cycloalkyl (particularly cyclopropyl) or haloalkyl (particularly dichloromethyl).

In another embodiment, R_1a and R_1b are independently selected from hydroxy, -NHC(=W)R_4, -OC(=O)R_4, and  ,

wherein W, R_4, R_5, R_6 and R_7 are as defined hereinbefore, especially wherein R_4 is (1-4C)alkyl or (1-4C)alkoxy.

Particular values for R_5 (which may be used as appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter) are hydrogen, tert-butoxycarbonyl and benzyloxycarbonyl. More particularly, R_5 is hydrogen.

When R_1a and/or R_1b is –N(R_5)HET-1, R_5 is preferably hydrogen.

In one aspect R_{12} and R_{13} are independently selected from hydrogen, alkyl and aryl, or for any N(R_{12})(R_{13}) group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring, optionally substituted as hereinbefore described. In one aspect R_{15} and R_{16} are independently selected from hydrogen, phenyl and (1-4C)alkyl).

In all of the embodiments, aspects and preferable values for R_1a and R_1b defined hereinbefore or hereinafter, any (1-4C)alkyl group may be optionally substituted as hereinbefore defined. Particular substituents for (1-4C)alkyl groups in definitions for R_1a and R_1b are one or two halogen groups, particularly geminal disubstitution (provided that such substitution is not on a carbon atom attached to an oxygen) and cyano. Examples of di-halosubstituted groups are –NHCOCF_2H and -NHCSCCl_2H.

Preferably R_1a and R_1b are independently selected from hydroxy, -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl, -NHCS(1-4C)alkyl, -NHCOO(1-4C)alkyl, -NH(C=S)O(1-4C)alkyl, -OCO(1-4C)alkyl, -N(R_5)-HET-1 and HET-2.

More preferably R_1a and R_1b are independently selected from -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl , -NHCS(1-4C)alkyl, -N(R_5)-HET-1 and HET-2.

In one embodiment R_1a and R_1b are independently selected from hydroxy, -NHCOMe, -NH(C=S)OMe and -NHCOOMe.

In a further embodiment R_1a is selected from hydroxy, -NHCO(1-4C)alkyl (especially –NHCOMe), -NHCO(1-4C)cycloalkyl (especially –NHCOcyclopropyl), -NHCS(1-4C)alkyl (especially –NHCSMe) , -NHCOO(1-4C)alkyl (especially –NHCO)Me), -NH(C=S)O(1-4C)alkyl (especially –NH(C=S)OMe) and -OCO(1-4C)alkyl (especially –OCOMe) and R_1b is HET-2.

In a further embodiment R_1a is selected from hydroxy, -NHCO(1-4C)alkyl (especially –NHCOMe), -NHCO(1-4C)cycloalkyl (especially –NHCOcyclopropyl), -NHCS(1-4C)alkyl (especially –NHCSMe) , -NHCOO(1-4C)alkyl (especially –NHCO)Me), -NH(C=S)O(1-4C)alkyl (especially –NH(C=S)OMe) and -OCO(1-4C)alkyl (especially –OCOMe) and R_1b is -N(R_5)-HET-1.

In another embodiment R_1a and R_1b are both -NHCO(1-4C)alkyl (especially –NHCOMe) or HET-2 (especially 1,2,3-triazol-1-yl or tetrazol-2-yl).

In a further embodiment R_1a is -NHCO(1-4C)alkyl (especially –NHCOMe) and R_1b is HET-2 (especially 1,2,3-triazol-1-yl or tetrazol-2-yl).

In a further embodiment R1a is hydroxy and R1b is selected from -NHCO(1-4C)alkyl (especially –NHCOMe), -NHCO(1-4C)cycloalkyl (especially –NHCOcyclopropyl), -NHCS(1-4C)alkyl (especially –NHCSMe) , -NHCOO(1-4C)alkyl (especially –NHCO)Me), -NH(C=S)O(1-4C)alkyl (especially –NH(C=S)OMe) and -OCO(1-4C)alkyl (especially –OCOMe), -N(R_5)-HET-1 (especially where HET-1 is isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl) and HET-2 (especially 1,2,3-triazol-1-yl or tetrazol-2-yl).

In a further embodiment, R_1a and R_1b are independently selected from hydroxy, acetamido, 1,2,3-triazol-1-yl, methyl-1,2,3-triazol-1-yl and isoxazolylamino.

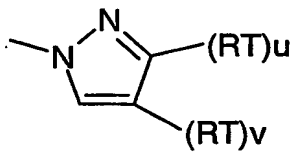
In one embodiment HET-1 and HET-2 are unsubstituted. When substituted, preferred substituents for HET-1 are selected from (1-4C)alkyl, especially methyl, and for HET-2 are selected from halo (particularly chloro), (1-4C)alkyl, especially methyl, mono- and di-halo methyl (wherein halo is preferably fluoro, chloro or bromo), trifluoromethyl and cyanomethyl.

Preferred are HET-1 and HET-2 as 5-membered rings, ie HET-1 as HET-1A and HET_2 as HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl or tetrazol-2-yl.

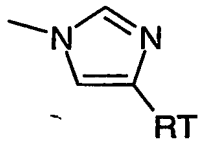
In one aspect, HET-2A as 1,2,3-triazol-1-yl is substituted, preferably by halo

(particularly chloro), methyl, difluoromethyl, fluoromethyl, chloromethyl, cyanomethyl or trifluoromethyl.

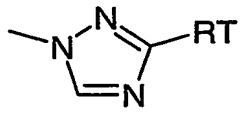
In one embodiment HET-2A is selected from the structures (Za) to (Zf) below:



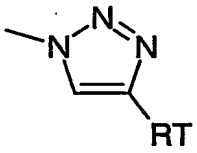
(Za)



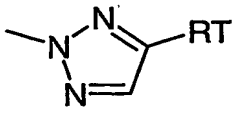
(Zb)



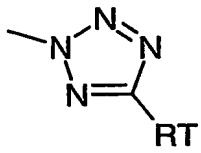
(Zc)



(Zd)



(Ze)



(Zf)

wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In one embodiment HET-2A is selected from 1,2,3-triazole (especially 1,2,3-triazol-1-yl (Zd)), 1,2,4-triazole (especially 1,2,4-triazol-1-yl (Zc)) and tetrazole (preferably tetrazol-2-yl (Zf)) and wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2A is selected from 1,2,3-triazol-1-yl (Zd) and tetrazol-2-yl (Zf) and wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2A is 1,2,3-triazol-1-yl (Zd) and wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In one embodiment HET-2B is a di-hydro version of pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine and pyridine and wherein RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2B is selected from pyrimidone, pyridazinone, pyrazinone, 1,2,3-triazinone, 1,2,4-triazinone, 1,3,5-triazinone and pyridone and wherein RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2B is selected from thiopyrimidone, thiopyridazinone, thiopyrazinone, thio-1,2,3-triazinone, thio-1,2,4-triazinone, thio-1,3,5-triazinone and thiopyridone and wherein RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In one aspect RT is preferably selected from a substituent from the group

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro;or,

(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino and (2-4C)alkenylamino;

(RTb1) a (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or

(RTb2) a (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl and (3-6C)cycloalkenyl;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), or (RTb1) or (RTb2) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN.

In another aspect RT is preferably selected from a substituent from the group:

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano, and nitro; or

(RTb1) a (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTb1) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, and CN.

In a further aspect RT is most preferably

(a) hydrogen; or

(b) halogen, in particular fluorine, chlorine, or bromine; or

(c) cyano; or

(d) (1-4C)alkyl, in particular methyl; or

(e) monosubstituted (1-4C)alkyl, in particular fluoromethyl, choromethyl, bromomethyl, cyanomethyl, azidomethyl, hydroxymethyl; or

(f) disubstituted (1-4C)alkyl, for example difluoromethyl, or trisubstituted (1-4C)alkyl, for example trifluoromethyl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-

acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-

acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a and R_1b are independently selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In another embodiment is provided a compound of formula (I) or a pharmaceutically-

acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a and R_1b are independently selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; A and B are both oxazolidinones; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a is selected

from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; B is an isoxazoline and A is an oxazolidinone; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group D, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group E, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is group H, R_2b and R_6b are independently H or F; A is an isoxazoline and B is an oxazolidinone; R_1a is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and –NHCOOMe and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In all of the above definitions the preferred compounds are as shown in formula (IA),

i.e. the pharmaceutically active enantiomer.

Particular compounds of the present invention include each individual compound described in the Examples, especially Examples 2 and 4.

Process section:

In a further aspect the present invention provides a process for preparing a compound of invention or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group

for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon. Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A compound of the invention, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the invention, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March or Houben-Weyl, Methoden der Organischen Chemie). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the certain Patent Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference; for example WO 94-13649; WO 98-54161; WO 99-64416;

WO 99-64417; WO 00-21960; WO 01-40222.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products. For example, the skilled chemist will be able to apply the teaching herein for compounds of formula (I) in which two central phenyl groups are present (that is when group C is group D) to prepare compounds in which group C is any of groups E to O as hereinbefore defined. Similarly, in the processes illustrated below the skilled chemist will be able to apply the teaching as necessary to prepare compounds in which for instance both rings A and B are isoxazoline and those compounds in which one of rings A and B is isoxazoline and the other oxazolidinone.

Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and in-vivo hydrolysable esters thereof, can be prepared by a process (a) to (h) as follows (wherein the variables are as defined above unless otherwise stated):

a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry (see for example, Comprehensive Organic Functional Group Transformations (Pergamon), Katritzky, Meth-Cohn & Rees or Advanced Organic Chemistry (Wiley-Interscience), Jerry March or Houben-Weyl, Methoden der Organischen Chemie)); for example:

an acylamino group may be converted into a thioacylamino group;

an acylamino group or thioacylamino group may be converted into another acylamino or thioacylamino; heterocyclyl for instance tetrazolyl or thiazolyl, or heterocyclylamino group (optionally substituted or protected on the amino-nitrogen atom), a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon adjacent to the linking nitrogen atom), for instance an optionally 4-substituted 1,2,3-triazol-1-yl group; or an amidino group; such conversions of the acylamino group taking place either directly or through through the intermediacy of one or more derivatives such as an amino group;

an acyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group);

an alkyl halide such as alkylbromide or alkyliodide may be converted into an alkyl fluoride or nitrile;

an alkyl sulfonate such as alkyl methanesulfonate may be converted into an alkyl fluoride or nitrile;

an alkylthio group such as methylthio may be converted into a methanesulfinyl or methanesulfonyl group,

an arylthio group such as phentlthio may be converted into a benzenesulfinyl or benzenesulfonyl group,

an amidino or guanidino group may be converted into a range of 2-substituted 1,3-diazoles and 1,3-diazines

an amino group may be converted for instance into acylamino or thioacylamino for instance an acetamide (optionally substituted), alkyl- or dialkyl-amino and thence into a further range of N-alkyl-amine derivatives, sulfonylamino, sulfinylamino, amidino, guanidino, arylamino, heteroarylamino, N-linked heterocyclic for instance an optionally 4-substituted 1,2,3-triazol-1-yl group;

an aryl- or heteroary-halide group such as an aryl- or hetero-aryl chloride or bromide or iodide may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of aryl-, heteroaryl, alkenyl, alkynyl, acyl, alkylthio, or alkyl- or dialkyl-amino substituted aryl or heteroaryl groups;

an aryl- or heteroary-sulfonate group such as an aryl- or hetero-aryl trifluoromethanesulfonate may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of aryl-, heteroaryl, alkenyl, alkynyl, acyl, alkylthio, or alkyl- or dialkyl-amino substituted aryl or heteroaryl groups;

an aryl- or heteroary-halide group such as an aryl- or hetero-aryl chloride or bromide or iodide may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of trialkyltin, dialkylboronate, trialkoxysilyl, substituted aryl or heteroaryl groups useful as intermediates for the synthesis of compounds of the invention;

an azido group may be converted for instance into a 1,2,3-triazolyl or amine and thence by methods that are well known in the art into any of the range common amine derivatives.such as acylamino for instance acetamido group;

a carboxylic acid group may be converted into trifloromethyl, hydroxymethyl, alkoxycarbonyl, aminocarbonyl optionally substituted on nitrogen, formyl, or acyl groups;

a cyano group may be converted into a tetrazole, or an imidate, an amidine, an amidrazone, an N-hydroxyamidrazone, an amide, a thioamide, an ester, or an acid and thence by methods that

are well known in the art into any of the range of heterocycles derived from such nitrile derivatives;

a hydroxy group may be converted for instance into an alkoxy, cyano, azido, alkylthio, keto and oximino, fluoro, bromo, chloro, iodo, alkyl- or aryl-sulfonyloxy for instance trifluoromethanesulfonate, methanesulfonate, or tosylsulfonate, silyloxy ; acylamino or thioacylamino , for instance an acetamide (optionally substituted or protected on the amido-nitrogen atom); acyloxy, for instance an acetoxy; phosphono-oxy, heterocyclylamino (optionally substituted or protected on the amino-nitrogen atom), for instance an isoxazol-3-ylamino or a 1,2,5-thiadiazol-3-ylamino; heterocyclyl linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom), for instance an optionally 4-substituted 1,2,3-triazol-1-yl; or amidino, for instance an 1-(N-cyanoimino)ethylamino group; such conversions of the hydroxy group taking place directly (for instance by acylation or Mitsunobu reaction) or through the intermediacy of one or more derivatives (for instance a mesylate or an azide);

a keto group may be converted into a hydroxy, thiocarbonyl, oximino, or difluoro group;

a nitro-group may be converted into an amino group and thence by methods that are well known in the art into any of the range common amine derivatives.such as acylamino for instance acetamido group;

a silyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group);

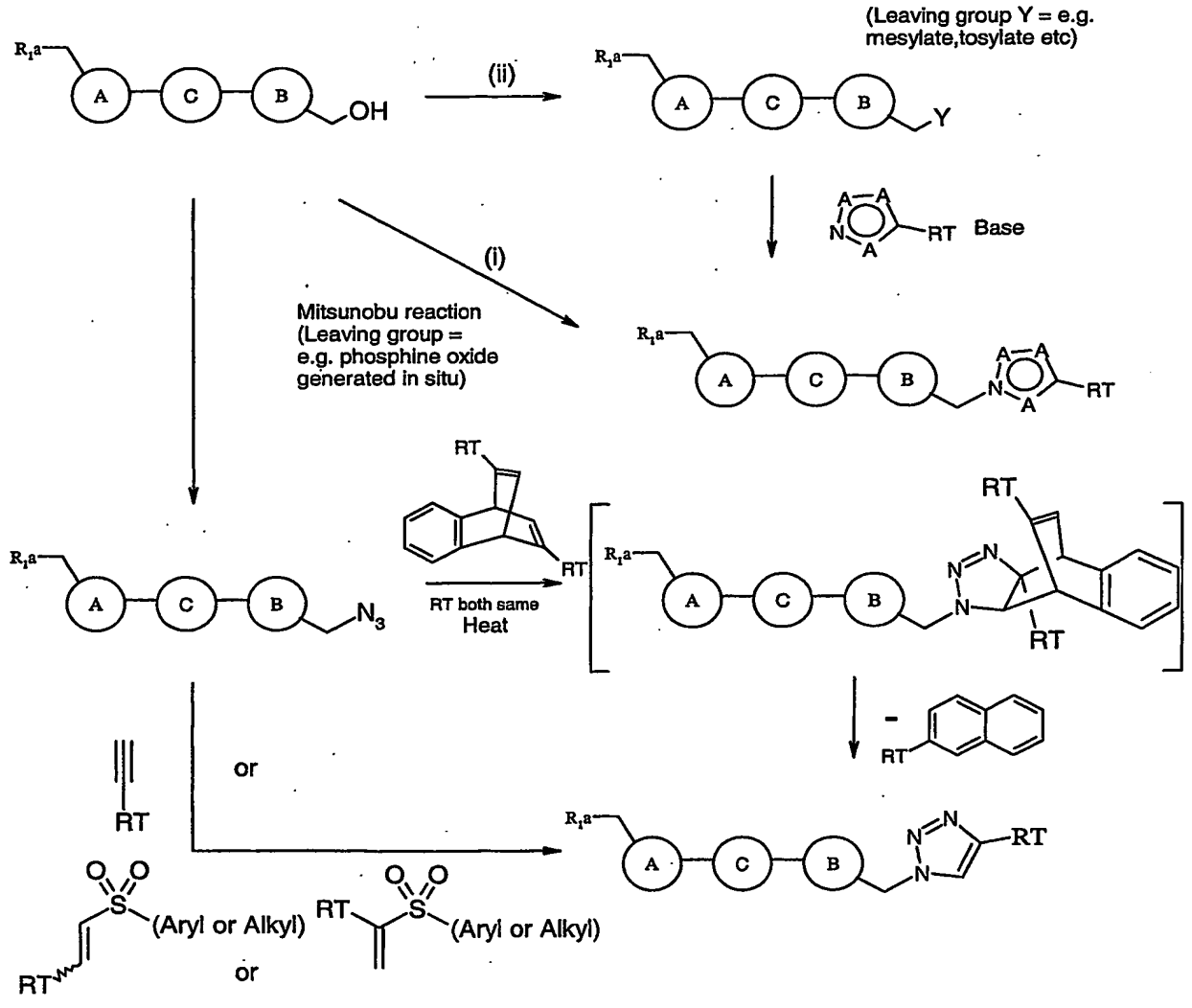
an optionally substituted aromatic or heteroaromatic ring C'may be converted into another aromatic or heteroaromatic ring C' by introduction of a new substituent (R2a to R6a or R2a' or R6a') or by refunctionalisation of an existing substituent (R2a to R6a or R2a' or R6a');

a heterocyclylamino group (optionally substituted or protected on the amino-nitrogen atom) may be converted into another heterocyclyl amino group (optionally substituted or protected on the amino-nitrogen atom) by refunctionalisation, for instance by protection or deprotection, of the amino-nitrogen atom, by introduction of a new ring substituent, or by refunctionalisation of an existing ring substituent; or

a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom) may be converted into another heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom) by introduction of a new ring

substituent or by refunctionalisation of an existing ring substituent, for instance by modifying the 4-substituent of a 4-substituted 1,2,3-triazol-1-yl group.

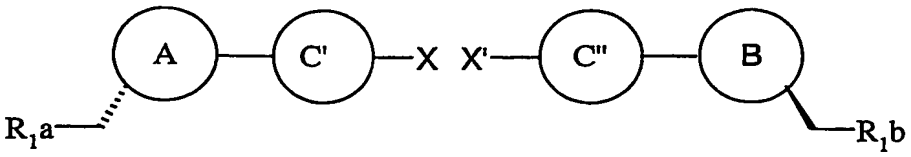
For instance, examples drawn from the methods for conversion of a hydroxy group into an optionally substituted triazole group are illustrated by the scheme:



Examples drawn from the range of regioselective methods that proceed under very mild conditions are further illustrated by processes (f), (g), and (h).

b) by reaction of a molecule of a compound of formula (IIa) (wherein X is a leaving group useful in palladium coupling, for example boronate, trimethyl tin, iodo and bromo) with a molecules of a compound of formula (IIb) (wherein X' is a leaving group useful in palladium coupling, for example boronate, trimethyl tin, iodo and bromo) wherein X and X' are chosen such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the

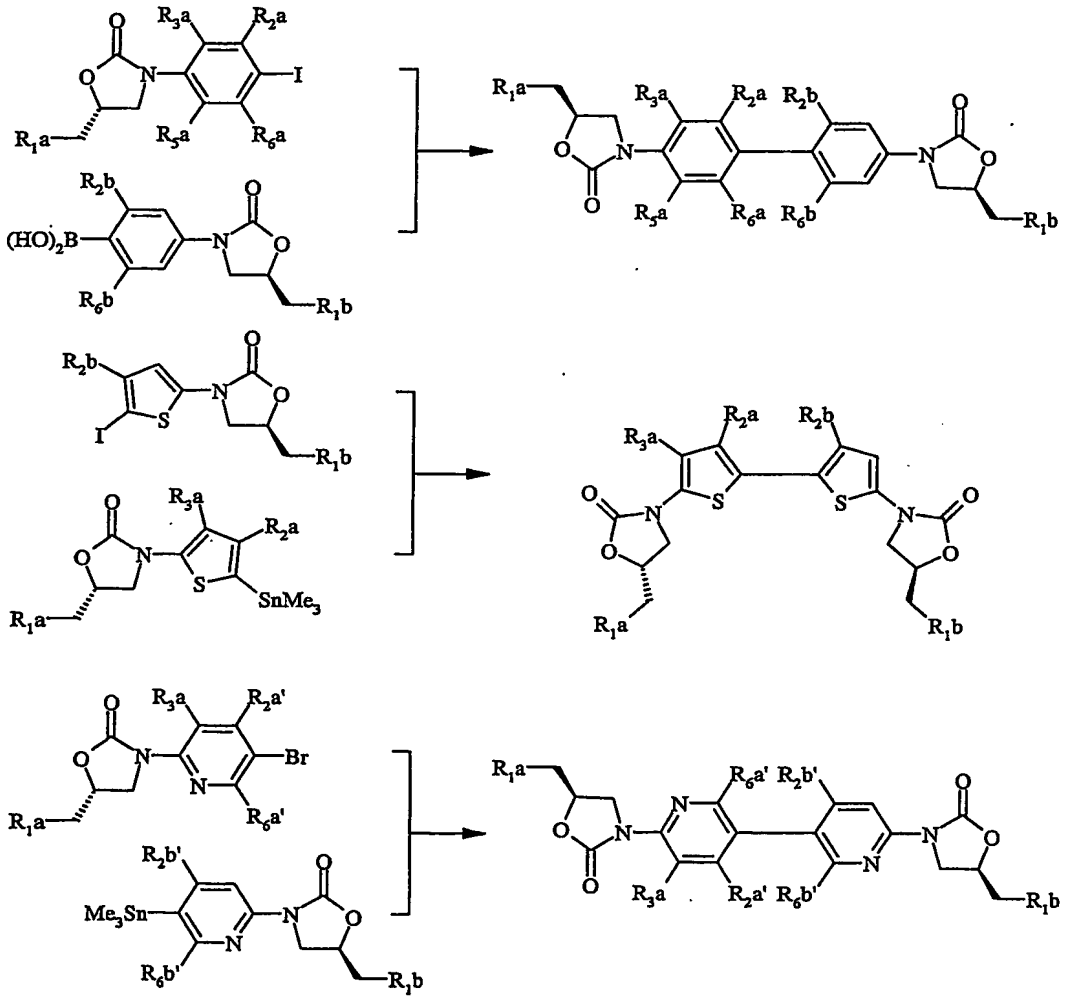
aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds. Such methods are now well known, see for instance S.P. Stanforth, Catalytic Cross-Coupling Reactions in Biaryl Synthesis, *Tetrahedron*, 54 **1998**, 263-303.

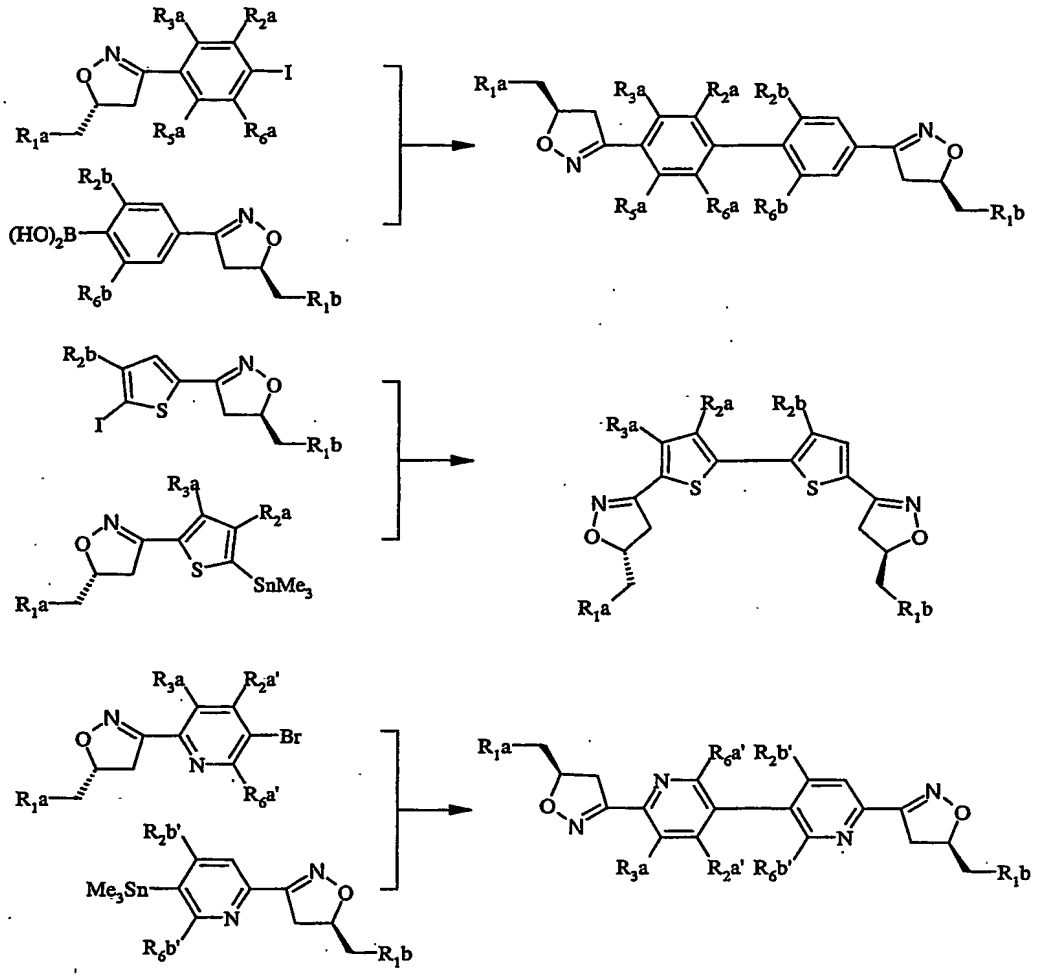


(IIa) **(IIb)**

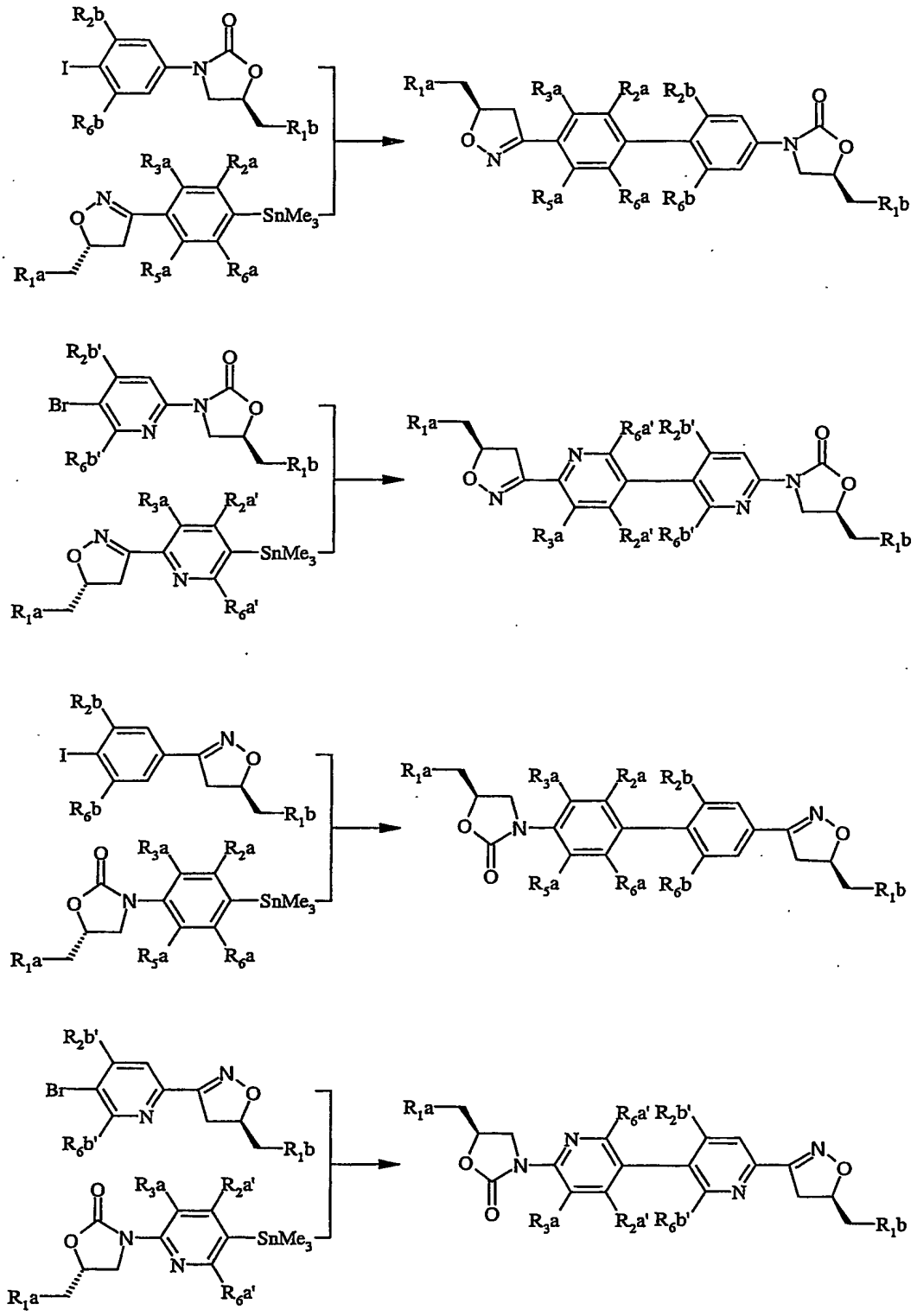
The leaving groups X and X' may be chosen to be the same and lead to symmetrical molecules of formula (I) or different and chosen to lead to symmetrical or unsymmetrical molecules of formula (I).

For example





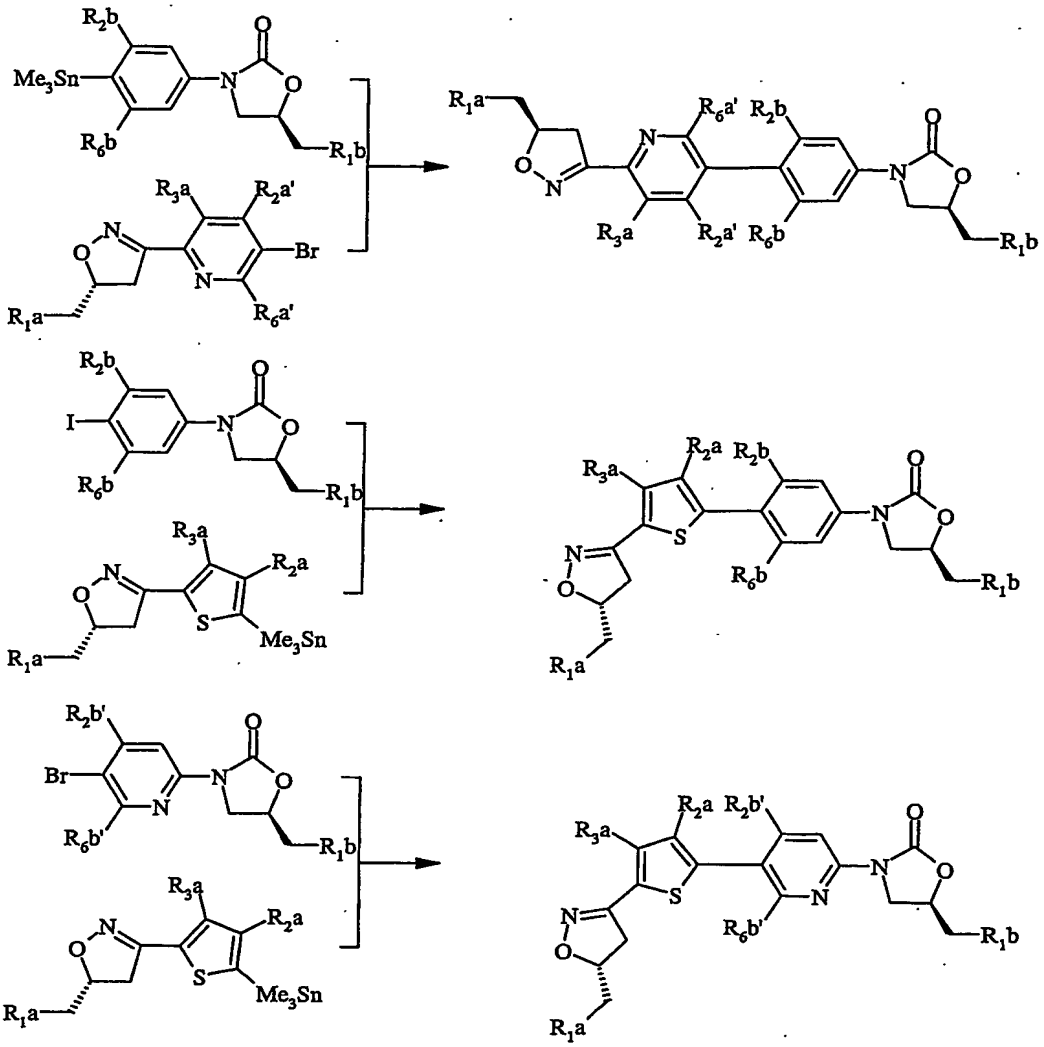
Similarly, this chemistry may be applied to two dissimilar molecules of formula (II), for example those in which ring A is not the same as ring B, wherein X is suitably selected to enable unsymmetrical coupling so that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and the aryl-X' (or heteroaryl-X') bonds. For example



Furthermore, this chemistry may also be applied to two dissimilar molecules of formula (II), for example those in which ring C' is not the same as ring C'', wherein X and X' are suitably selected to enable unsymmetrical coupling so that an aryl-aryl, heteroaryl-aryl, or heteroaryl-

heteroaryl bond replaces the two different aryl-X (or heteroaryl-X) and the aryl-X' (or heteroaryl-X') bonds.

For example



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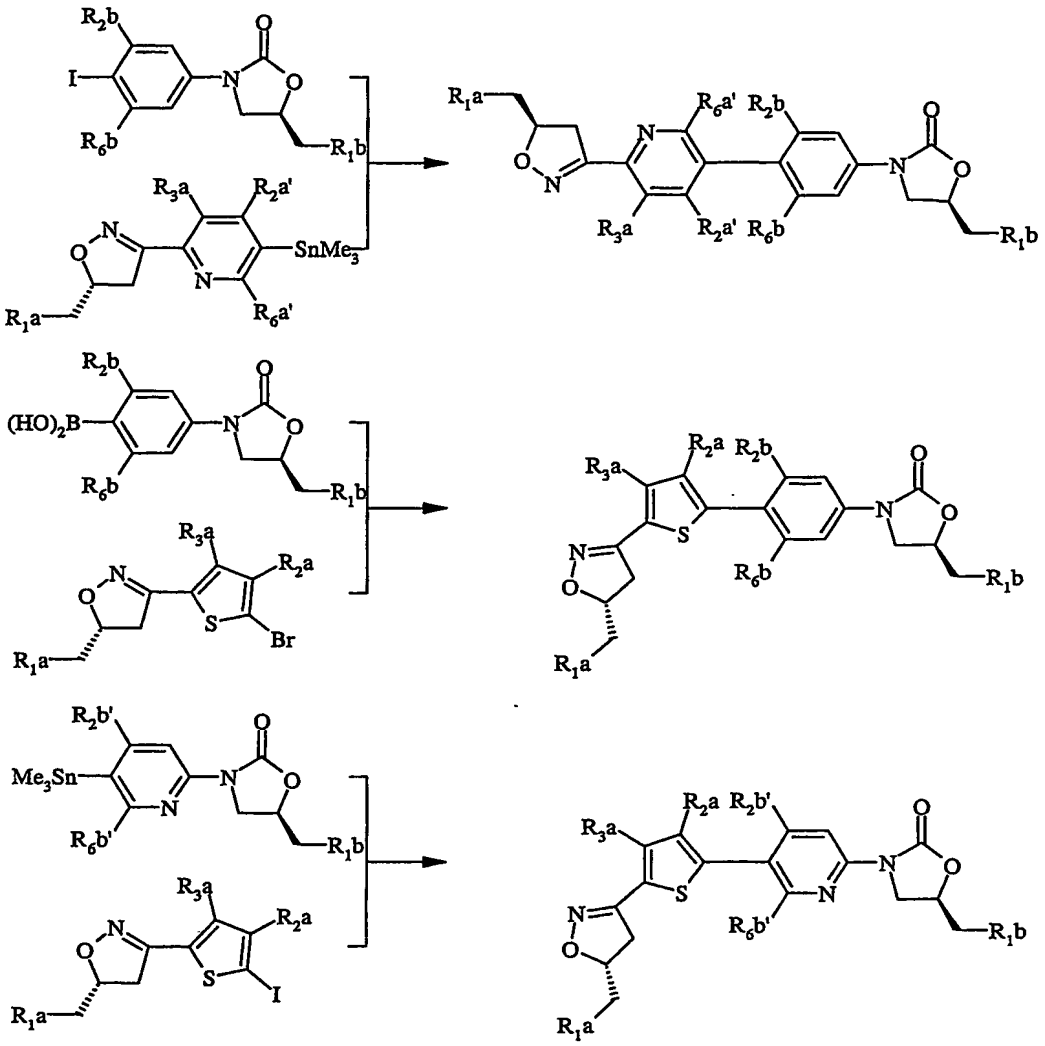
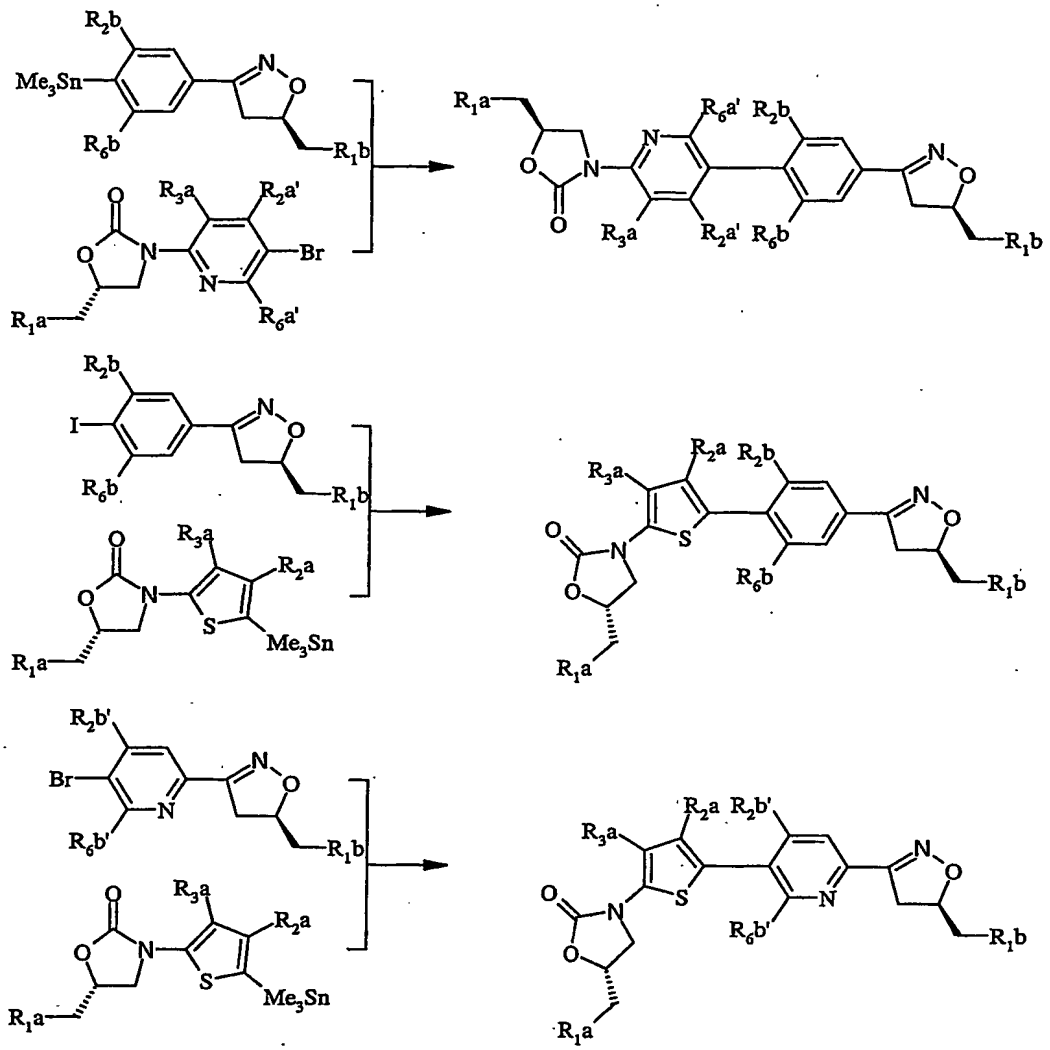
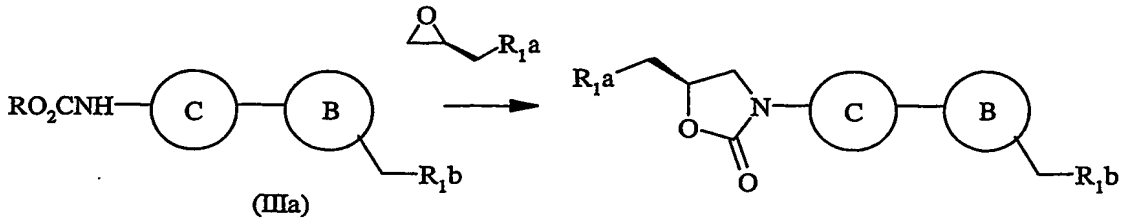


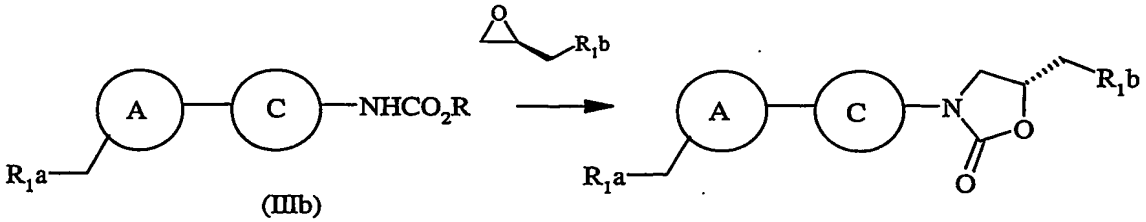


The aryl isoxazolines and aryl oxazolidiones required as reagents for process b) or as intermediates for the preparation of reagents for process b) may be prepared by standard organic methods, for instance by methods analogous to those set out in process sections c) to h). Methods for the introduction and interconversion of Groups X and X' are well known in the art.

c) by reaction of a (hetero)biaryl derivative (IIIa) or (IIIb) carbamate with an appropriately substituted oxirane to form an oxazolidinone ring at the undeveloped aryl position.



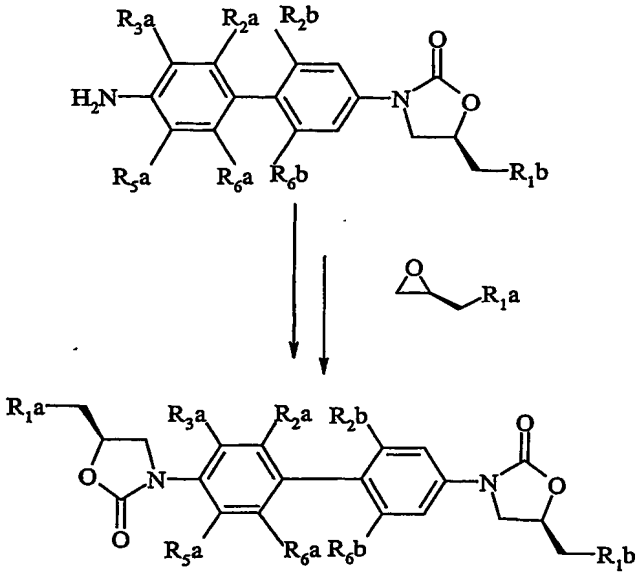
(IIIa)

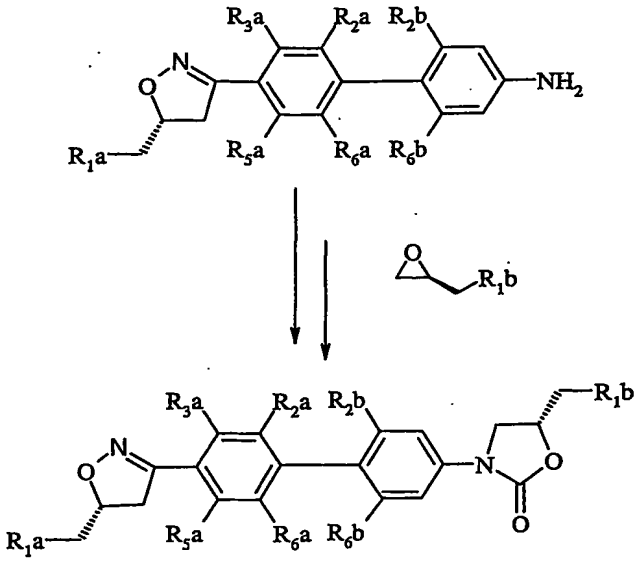


(IIIb)

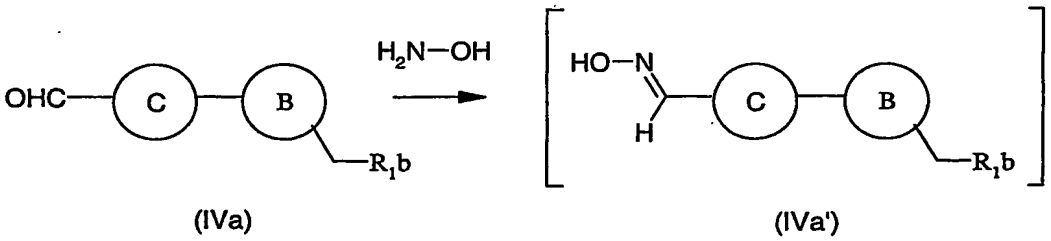
Variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-CH_2CH(O-optionally protected)CH_2R_1a or X-CH_2CH(O-optionally protected)CH_2R_1b where X is a displaceable group are also well known in the art.

For example,

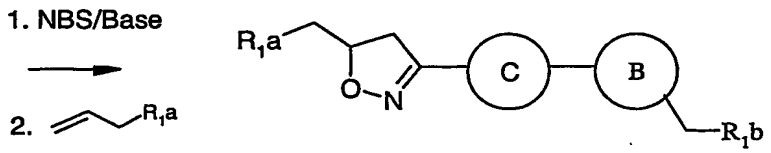


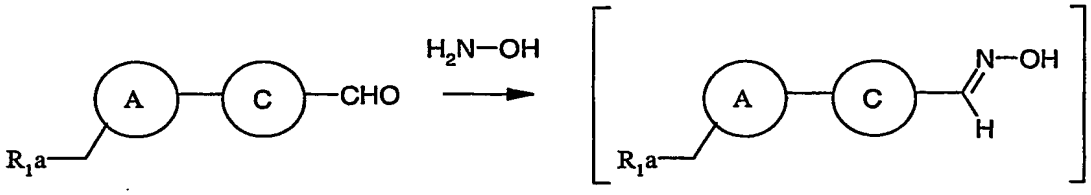


d) by reaction of a (hetero)biaryl derivative (IVa) or (IVb) to form an isoxazoline ring at the undeveloped aryl position.

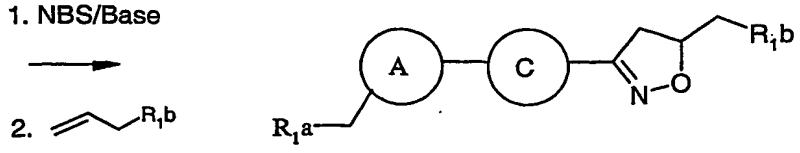


(IVa) (IVa')

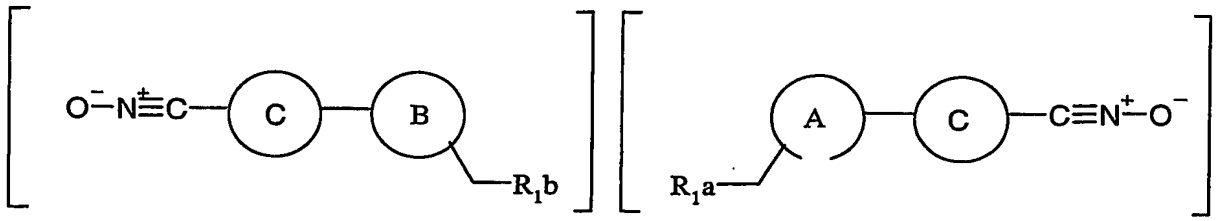




(IVb) (IVb')

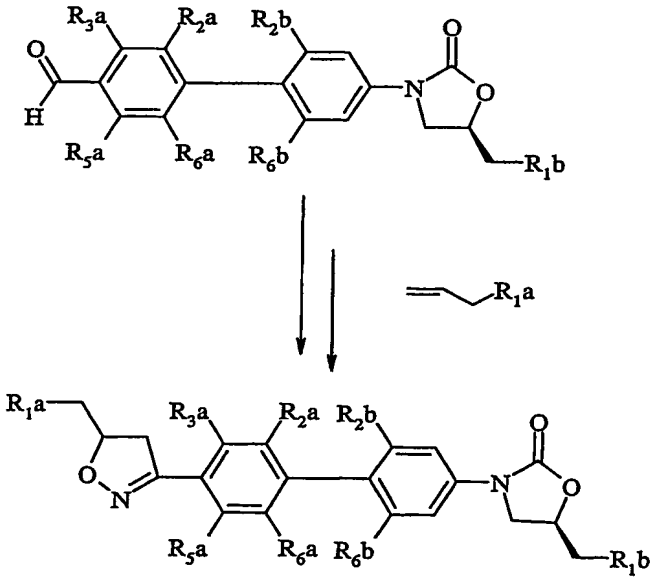


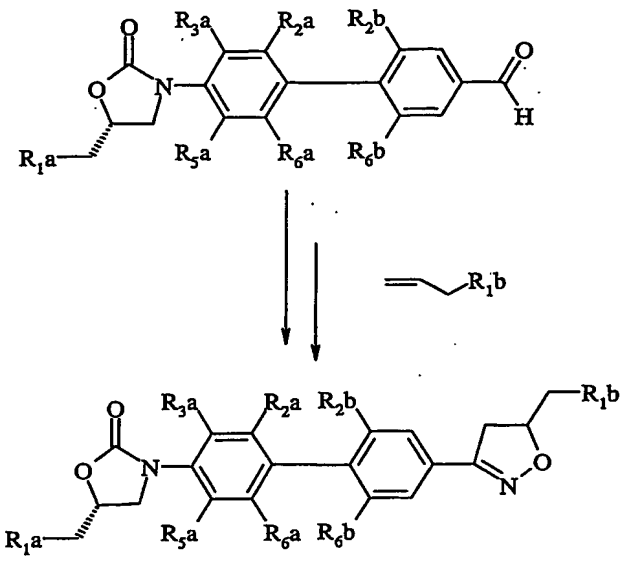
Variations on this process in which the reactive intermediate (a nitrile oxide IVa'' or IVb'') is obtained other than by oxidation of an oxime (IVa') or (IVb') are well known in the art.



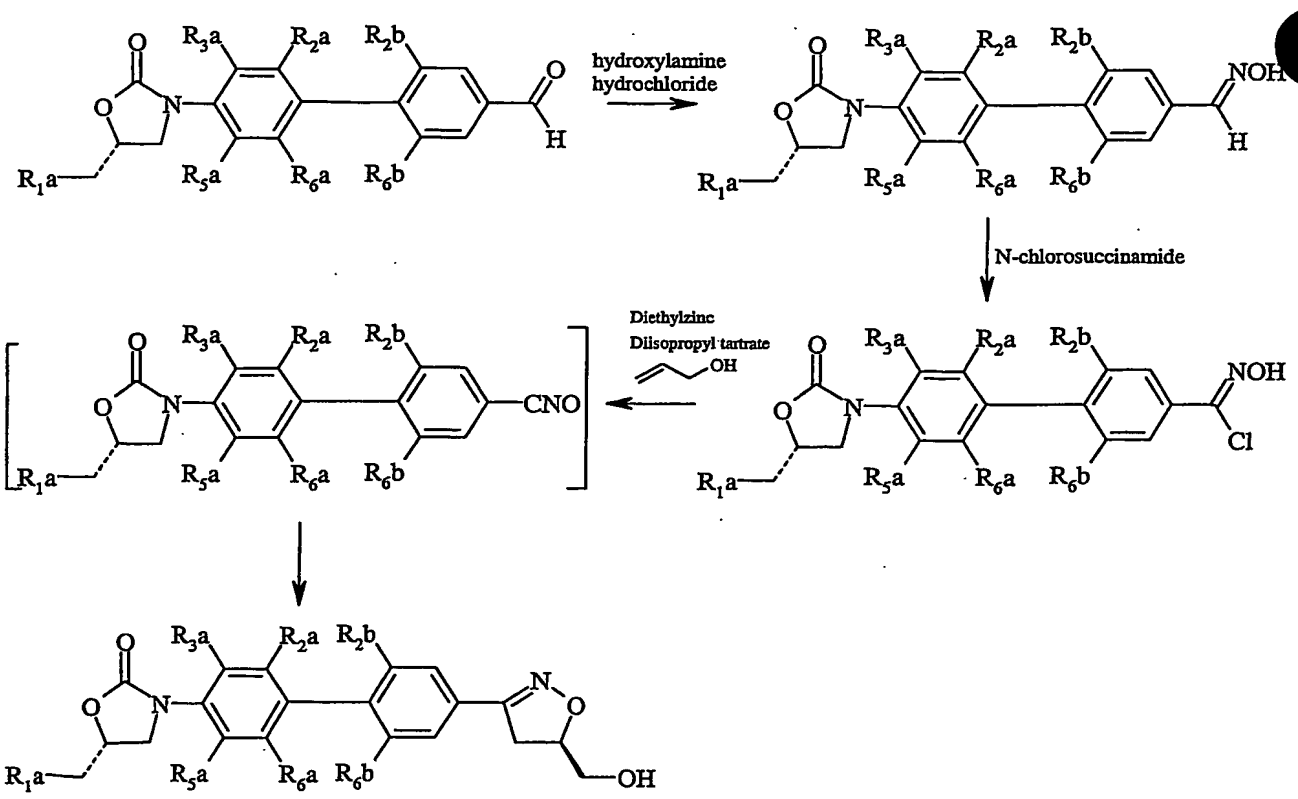
(IVa") (IVb")

For example, oxidation of an appropriately substituted biphenylcarboxaldehyde oxime in the presence of an appropriately substituted allyl derivative gives an isoxazoline of the required structure.



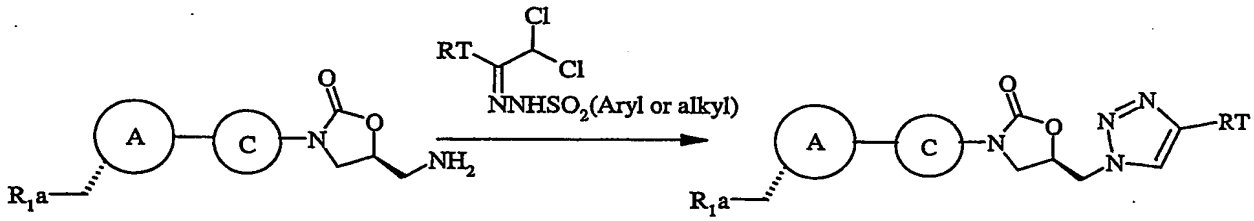


Enantioselective synthesis of 2-isoxazolines via asymmetric cycloaddition of nitrile oxides to olefins has been achieved by the use of chiral auxiliaries. For instance, when the alcohol is an allyl alcohol the desired stereochemistry at ring B can be obtained in reactions conducted in the presence of (*R,R*)-diisopropyl tartrate (or (*S,S*)-diisopropyl tartrate depending on the desired stereochemistry) as a chiral auxiliary (Yutaka Ukaji *et al. Chem. Letters*, **1993**, 1847-1850). Other chiral auxiliaries may also be employed with other olefins (see for instance Takahiko Akayama et al., Tet. Letters, 1992, 33, 5763-5766; and Jeffrey Stack et al., Tetrahedron, 1993, 49, 995-1008 and references therein).



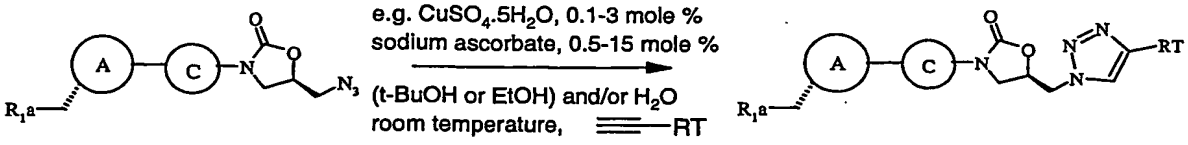
(e) for HET as optionally substituted 1,2,3-triazoles, compounds of the formula (I) may be made by cycloaddition via the azide (wherein e.g. Y in (II) is azide) to acetylenes, or to acetylene equivalents such as optionally substituted cylcohexa-1,4-dienes or optionally substituted ethylenes bearing eliminatable substituents such as arylsulfonyl; or

(f) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may be made by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones (Sakai, Kunihazu; Hida, Nobuko; Kondo, Kiyosi; *Bull. Chem. Soc. Jpn.*, **59**, *1986*, 179-183; Sakai, Kunikazu; Tsunemoto, Daiei; Kobori, Takeo; Kondo, Kiyoshi; Hido, Noboko EP 103840 A2 19840328); for instance

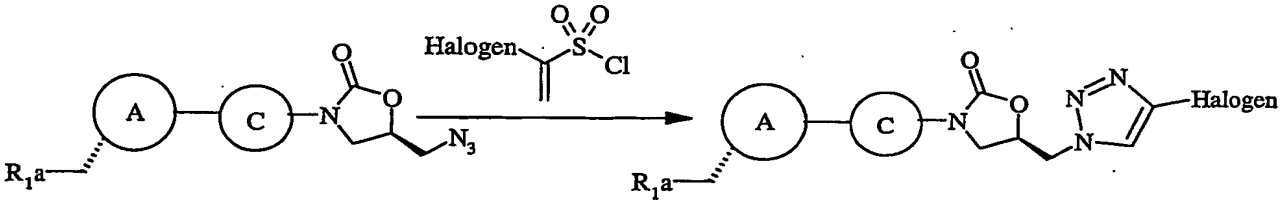


(g) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with terminal alkynes using Cu(I) catalysis in e.g. aqueous alcoholic solution at ambient temperatures to give 4-substituted 1,2,3-triazoles (V.V.

Rostovtsev, L.G. Green, V.V. Fokin, and K.B. Sharpless, Angew. Chem. Int. Ed., 2002, 41, 2596-2599): for instance



(h) for HET as 4-halogenated 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides at a temperature between 0 °C and 100 °C either neat or in an inert diluent such as chlorobenzene, chloroform or dioxan; for instance.



The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an in-vivo hydrolysable ester are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps, for example the preparation of in-vivo hydrolysable ester prodrugs has been provided, for example, in the section above on such esters.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the invention of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, aerosols (or sprays), drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of

this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 1mg and 1g of a compound of this invention, preferably between 100mg and 1g of a compound. Especially preferred is a tablet or capsule which contains between 50mg and 800mg of a compound of this invention, particularly in the range 100mg to 500mg.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example an injection which contains between 0.1% w/v and 50% w/v (between 1mg/ml and 500mg/ml) of a compound of this invention.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 0.5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention, the composition being administered 1 to 4 times per day. In another embodiment a daily dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention is administered. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

A pharmaceutical composition to be dosed intravenously may contain advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Antibacterial Activity :

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity

against enterococci, pneumococci and methicillin resistant strains of S.aureus and coagulase negative staphylococci, together with haemophilus and moraxella strains. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The (antibacterial) properties of the compounds of the invention may also be demonstrated and assessed in-vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal using standard techniques.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot. Typically, compounds are active in the range 0.01 to 256 μg/ml.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms. Fastidious Gram negative organisms were tested in Mueller-Hinton broth, supplemented with hemin and NAD, grown aerobically for 24 hours at 37°C, and with an innoculum of $5x10^4$ CFU/well.

For example, the following results were obtained for the compound of Example 4:

Organism		MIC (μg/ml)
Staphylococcus aureus:	MSQS	0.5
	MRQR	0.5
Streptococcus pneumoniae		0.13
Haemophilus influenzae		4
Moraxella catarrhalis		0.5
Enterococcus faecium		0.5
Linezolid Resistant Streptococcus pneumoniae		1

MSQS = methicillin sensitive and quinolone sensitive

MRQR = methicillin resistant and quinolone resistant

Certain intermediates and/or Reference Examples described hereinafter are within the scope of the invention and may also possess useful activity, and are provided as a further feature of the invention.

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in-vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-d_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]; optical rotations were determined at 589nm at 20°C for 0.1M solutions in methanol using a Perkin Elmer Polarimeter 341;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

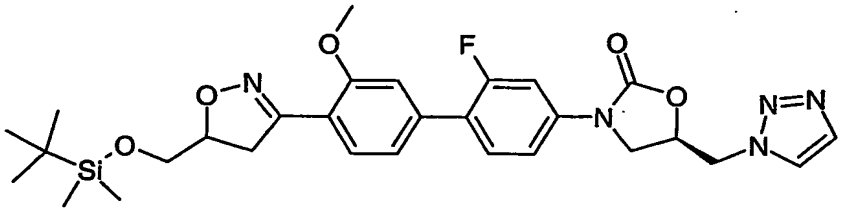
(vii) in which the following abbreviations may be used :-

DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is

mass spectroscopy; ESP is electrospray; EI is electron impact; CI is chemical ionisation; APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; phosphiryl is $(HO)_2$-P-O-; Bleach is "Clorox" 6.15% sodium hypochlorite;

(viii) temperatures are quoted as °C.

Example 1. (5*R*)-3-{4'-[5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-3'-methoxy-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



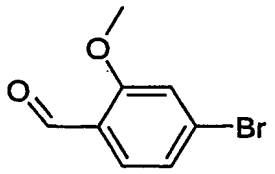
A stirred mixture of (5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (186 mg, 0.48 mmol), 5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-[2-methoxy-4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole (255 mg, 0.53 mmol) and copper (I) iodide (38 mg, 0.20 mmol) in dry 1-methyl-2-pyrrolidinone (2 mL) was degassed and then treated under argon with *tetrakis*(triphenylphosphine)palladium(0) (55 mg, 0.05 mmol). The reaction mixture stirred for 16 hours at 90°C and then cooled and partitioned between water (20 mL) and ethyl acetate (20 mL). The ethyl acetate layer was separated, dried over magnesium sulphate, filtered and the product was concentrated *in vacuo* onto Isolute HM-N (4 mL). The product was purified by by chromatography on silica-gel [SiO_2 20g bond elut: elution gradient from 10% to 50% *iso*-propanol:hexanes] to give the title compound (89 mg, 32%).

MS (ESP+): $(M+H)^+$ 582.11 for $C_{29}H_{36}FN_5O_5Si$

NMR (DMSO-d_6) δ: 0.07 (s, 3H); 0.09 (s, 3H); 0.86 (s, 9H); 3.24 (dd, 1H); 3.47 (dd, 1H); 3.69 to 3.79 (m, 2H); 3.80 (s, 3H); 3.96 (dd, 1H); 4.31 (t, 1H); 4.85 (m, 1H); 4.87 (d, 2H); 5.19 (m, 1H); 7.30 to 7.42 (m, 5H); 7.49 (m, 1H); 7.80 (m, 1H); 8.21 (s, 1H).

The intermediates for these compounds were prepared as follows :-

4-Bromo-2-methoxybenzaldehyde

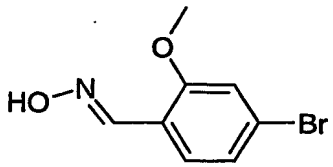


A stirred solution of 4-bromo-2-hydroxybenzaldehyde (1.035 g, 5.12 mmol) in anhydrous acetone (75 mL) was treated with potassium carbonate (0.865 g, 6.26 mmol) and dimethylsulphate (0.44 mL , 4.6 mmol) and then heated under reflux for 90 minutes. The reaction mixture was filtered and the product was then concentrated *in vacuo* onto Isolute HM-N (10 mL). The product was purified by by chromatography on silica-gel [SiO_2 50g bond elut: elution gradient 0% to 25% ethyl acetate:hexanes] to give the title compound (0.616 g, 56%).

MS (APCI+): $(M+acetonitrile)^+$ 256 & 258 for $C_8H_7BrO_2$

NMR (DMSO-d_6) δ: 3.95 (s, 3H); 7.18 (dd, 1H); 7.28 (d, 1H); 7.98 (d, 1H); 9.94 (s, 1H).

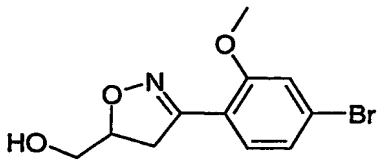
4-Bromo-2-methoxybenzaldehyde oxime



A stirred solution of 4-bromo-3-methoxybenzaldehyde (0.616 g, 2.86 mmol) in methanol (20 mL) and water (2 mL) was treated with hydroxylamine hydrochloride (0.234 g, 3.44 mmol) and sodium carbonate (0.182 g, 1.72 mmol). The reaction mixture was stirred at room temperature for 16 hours then the methanol removed *in vacuo*. The involatile residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The ethyl acetate layer was separated, dried over magnesium sulphate, filtered, and the product was concentrated *in vacuo* onto Isolute HM-N (5 mL). The product was purified by by chromatography on silica-gel [SiO_2 20g bond elut: elution gradient 0% to 25% ethyl acetate:hexanes] to give the title compound (324 mg 49%).

NMR (DMSO-d_6) δ: 3.90 (s, 3H); 6.83 (dd, 1H); 7.09 (d, 1H); 7.27 (br s, 1H); 7.76 (d, 1H); 8.07 (s, 1H).

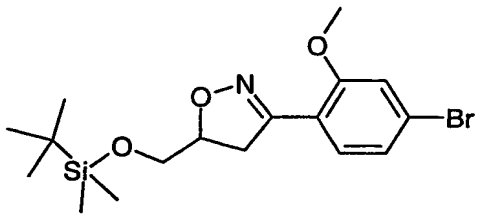
[3-(4-Bromo-2-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol



A stirred solution of 4-bromo-2-methoxybenzaldehyde oxime (320 mg, 1.4 mmol) in tetrahydrofuran (2 mL) was treated at room temperature with allyl alcohol (0.14 mL , 2.1 mmol) and then with household bleach ("Clorox" 6.15% sodium hypochlorite; 10 mL). The reaction mixture was stirred at room temperature for 16 hours and then extracted with ethyl acetate (20 mL). The ethyl acetate layer was separated, dried over magnesium sulphate, filtered, and then the product was concentrated *in vacuo* onto Isolute HM-N (5 mL). The product was purified by column chromatography [SiO_2 10g bond elut: elution gradient 50% to 100% ethyl acetate:hexanes] to give the title compound (239 mg 60%).

NMR (DMSO-d_6) δ: 3.23 (dd, 1H); 3.39 to 3.55 (m, 3H); 3.89 (s, 3H); 4.74 (m, 1H); 5.02 (t, 1H); 7.04 (dd, 1H); 7.23 (d, 1H); 7.86 (d, 1H).

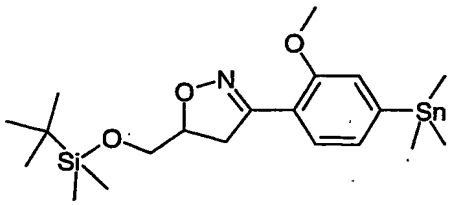
3-(4-Bromo-2-methoxyphenyl)-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole



A solution of [3-(4-Bromo-2-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol (0.239 g, 0.84 mmol) in a mixture of triethylamine (0.14 mL , 1.0 mmol) and dichloromethane (10 mL) was treated dropwise during 5 minutes with a solution of *tert*-butyldimethylsilylchloride (1M , 0.92 mL) in dichloromethane and then with 4-dimethylaminopyridine (10 mg, 0.084 mmol). The reaction mixture was stirred overnight at room temperature and then concentrated *in vacuo* onto Isolute HM-N (3 mL). The product was purified by chromatography [SiO_2 20g bond elut; elution gradient 0% to 25% ethyl acetate:hexanes] to give the title compound (0.27 g 81%) as a white crystalline solid.

NMR (DMSO-d_6) δ: 0.05 (s, 3H); 0.07 (s, 3H); 0.84 (s, 9H); 3.20 (dd, 1H); 3.46 (dd, 1H); 3.67 to 3.79 (m, 2H); 3.88 (s, 3H); 4.79 (m, 1H); 7.02 (dd, 1H); 7.22 (d, 2H); 7.85 (d, 1H).

5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-[2-methoxy-4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole

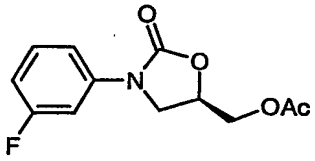


A stirred solution of 3-(4-bromo-2-methoxyphenyl)-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole (0.27 g, 0.67 mmol) in dry 1,4-dioxane (6 mL) was degassed and maintained under an atmosphere of argon. The mixture was treated with hexamethylditin (0.265 g, 0.81 mmol) and then with *bis*(triphenylphosphine)palladium(II) chloride (0.024 g, 0.03 mmol). The reaction mixture was stirred at 90°C for 180 minutes under an atmosphere of argon. The solvent was removed *in vacuo*, the crude product was re-dissolved in hexanes (10 mL) and filtered to remove insoluble material. The hexane solution of the product was purified by chromatography [SiO_2 10g bond elut: elution gradient 0% to 20% ethyl acetate:hexanes] to give the title compound (0.255 g 78%) as an oil.

MS (ESP+): $(M+H)^+$ 481.89, 483.96, 485.83, 487.83 & 489.90 for $C_{20}H_{35}NO_3SiSn$

NMR (DMSO-d_6) δ: 0.06 (s, 3H); 0.07 (s, 3H); 0.26 (t, 9H); 0.85 (s, 9H); 3.18 (dd, 1H); 3.44 (dd, 1H); 3.66 to 3.79 (d, 2H); 3.80 (s, 3H); 4.77 (m, 1H); 7.14 to 7.24 (m, 2H); 7.39 (d, 1H).

Acetic acid (5*R*)-3-(3-fluorophenyl)-1,3-oxazolidin-2-on-5-ylmethyl ester

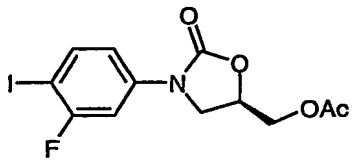


(5*R*)-3-(3-Fluorophenyl)-5-hydroxymethyl-1,3-oxazolidin-2-one (40 g, 0.189 M, see Upjohn WO 94-13649) was suspended by stirring in dry dichloromethane (400 mL) under nitrogen. Triethylamine (21 g, 0.208 M) and 4-dimethylaminopyridine (0.6 g, 4.9 mM) were added, followed by dropwise addition of acetic anhydride (20.3 g, 0.199 M) over 30 minutes, and stirring continued at ambient temperature for 18 hours. Saturated aqueous sodium bicarbonate (250 mL) was added, the organic phase separated, washed with 2% sodium dihydrogen phosphate, dried (magnesium sulfate), filtered and evaporated to give the desired product (49.6 g) as an oil.

MS (ESP): 254 (MH^+) for $C_{12}H_{12}FNO_4$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 3.84 (dd, 1H); 4.16 (t, 1H); 4.25 (dd, 1H); 4.32 (dd, 1H); 4.95 (m, 1H); 6.95 (td, 1H); 7.32 (d, 1H); 7.43 (t, 1H) ; 7.51 (d, 1H).

Acetic acid (5*R*)-3-(3-fluoro-4-iodo-phenyl)-1,3-oxazolidin-2-one-5-ylmethyl ester

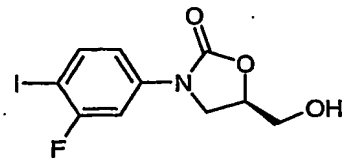


Acetic acid (5*R*)-3-(3-fluoro-phenyl)-1,3-oxazolidin-2-one-5-ylmethyl ester (15.2 g, 60 mM) was dissolved in a mixture of chloroform (100 mL) and acetonitrile (100 mL) under nitrogen, and silver trifluoroacetate (16.96 g, 77 mM) added. Iodine (18.07 g, 71 mM) was added in portions over 30 minutes to the vigorously stirred solution, and stirring continued at ambient temperature for 18 hours. As reaction was not complete, a further portion of silver trifluoroacetate (2.64 g, 12 mM) was added and stirring continued for 18 hours. After filtration, the mixture was added to sodium thiosulfate solution (3%, 200 mL) and dichloromethane (200 mL), and the organic phase separated, washed with sodium thiosulfate (200 mL), saturated aqueous sodium bicarbonate (200 mL), brine (200 mL), dried (magnesium sulfate), filtered and evaporated. The crude product was suspended in *iso*hexane (100 mL), and sufficient diethyl ether added to dissolve out the brown impurity while stirring for 1 hour. The product was isolated by filtration to give the title compound (24.3 g) as a cream solid.

MS (ESP): 380 (MH^+) for $C_{12}H_{11}FINO_4$

NMR (DMSO-d_6) δ: 2.03 (s, 3H); 3.82 (dd, 1H); 4.15 (t, 1H); 4.24 (dd, 1H); 4.30 (dd, 1H); 4.94 (m, 1H); 7.19 (dd, 1H); 7.55 (dd, 1H); 7.84 (t, 1H).

(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-hydroxymethyl-1,3-oxazolidin-2-one



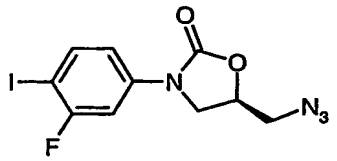
A solution of acetic acid (5*R*)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one-5-ylmethyl ester (30 g, 79 mM) in a mixture of methanol (800 mL) and dichloromethane (240 mL) was treated at ambient temperature with potassium carbonate (16.4 g, 0.119 mM) for 25 minutes,

then immediately neutralised by the addition of acetic acid (10 mL) and water (500 mL). The precipitated product was filtered, washed with water, and then dissolved in dichloromethane (1.2 L) to give a the solution that was washed with saturated sodium bicarbonate and then dried (magnesium sulfate). The solution of product was filtered and evaporated to dryness to give the title compound (23 g).

MS (ESP): 338 (MH^+) for $C_{10}H_9FINO_3$

NMR (DMSO-d_6) δ: 3.53 (m, 1H); 3.67 (m, 1H); 3.82 (dd, 1H); 4.07 (t, 1H); 4.70 (m, 1H); 5.20 (t, 1H); 7.21 (dd, 1H); 7.57 (dd, 1H); 7.81 (t, 1H).

(5*R*)-5-Azidomethyl-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one

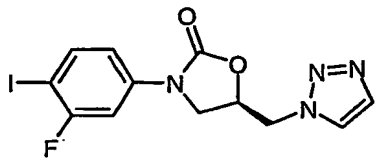


A stirred solution of (5*R*)-3-(3-fluoro-4-iodophenyl)-5-hydroxymethyl-1,3-oxazolidin-2-one (55.8 g) and triethylamine (46.1 mL) in dry dichloromethane (800 mL) under an atmosphere of dry nitrogen was maintained below room temperature by an ice-bath and treated dropwise with methanesulfonyl chloride (17.9 mL). The stirred reaction mixture was allowed to warm to room temperature during 3 hours and then washed sequentially with water and brine and then dried (Na_2SO_4). Solvent was removed under reduced pressure to give the intermediate mesylate as a yellow solid (68 g) that was used without further purification.

A stirred solution in DMF (800 mL) of a mixture of the intermediate mesylate (68 g) and sodium azide (32.3 g) was heated at 75°C overnight. The mixture was allowed to cool to room temperature, diluted with water, and extracted twice with ethyl acetate. The combined extracts were washed sequentially with water and brine, and then dried (Na_2SO_4). Solvent was removed under reduced pressure to give a yellow oil that was purified by column chromatography on silica-gel [elution with ethyl acetate:hexanes (1:1)] to give the product azide as an off-white solid (49 g). The product could be further purified by trituration with ethyl acetate/hexanes.

^{1}H-NMR (DMSO-d_6) δ: 3.57-3.64 (dd, 1H); 3.70-3.77 (dd, 1H); 3.81-3.87 (dd, 1H); 4.06 (t, 1H); 4.78-4.84 (m, 1H); 7.05-7.09 (ddd, 1H); 7.45 (dd, 1H); 7.68-7.74 (dd, 1H).

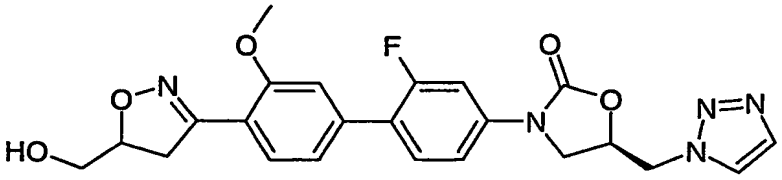
(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



A stirred solution in dioxan (300 mL) of a mixture of the (5*R*)-5-azidomethyl-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (30 g) and bicyclo[2.2.1]heptadiene (30 mL) was heated under reflux overnight. The mixture was allowed to cool to room temperature and then evaporated to dryness under reduced pressure to give a brown solid. The brown solid was purified by column chromatography on silica-gel [elution with a gradient from 98:2 to 95:5 methanol:chloroform] to give the product triazole as a pale yellow solid (20 g). The product could be further purified by trituration with dichloromethane/hexanes (1:1) to give an off-white solid.

^{1}H-NMR (DMSO-d_6) δ: 3.86-3.92 (dd, 1H); 4.23 (t, 1H); 4.83 (d, 2H); 5.11-5.19 (m, 1H); 7.12-7.16 (dd, 1H); 7.47-7.51 (dd, 1H); 7.76 (s, 1H); 7.79-7.85 (dd, 1H); 8.16 (s, 1H).

Example 2. (5*R*)-3-{2-Fluoro-4'-[5-(hydroxymethyl)-4,5-dihydroisoxazol-3-yl]-3'-methoxy-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one

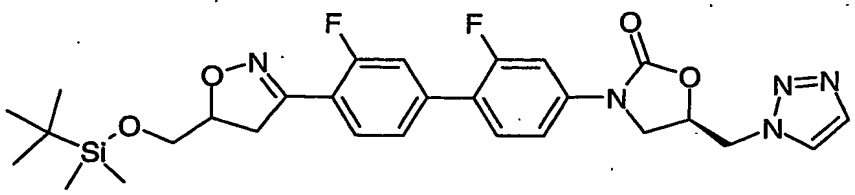


A solution of (5*R*)-3-{4'-[5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-3'-methoxy-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (87 mg, 0.15 mmol) in tetrahydrofuran (2 mL) at room temperature was treated with a solution of tetrabutylammonium fluoride in tetrahydrofuran (1M; 0.18 mL , 0.18 mmol). The reaction mixture was stirred for 120 minutes then concentrated *in vacuo*. The resulting solid was dissolved in DMSO (2 mL) and purified by reverse phase HPLC (elution gradient 30% to 50% acetonitrile:water) to give a white solid that was washed with saturated sodium hydrogen carbonate solution and then dried to give the title compound 34 mg (49%).

MS (ESP+): $(M+H)^+$ 468.00 for $C_{23}H_{22}FN_5O_5$

NMR (DMSO-d_6) δ: 3.26 (dd, 1H); 3.45 (dd, 1H); 3.55 (d, 2H); 3.81 (s, 3H); 3.96 (dd, 1H); 4.31 (t, 1H); 4.76 (m, 1H); 4.88 (d, 2H); 5.05 (s, 1H); 5.20 (m, 1H); 7.32 to 7.42 (m, 5H); 7.47 to 7.51 (dd, 1H); 7.80 (s, 1H); 8.21 (d, 1H).

Example 3. (5*R*)-3-{4'-[5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2,3'-difluoro-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



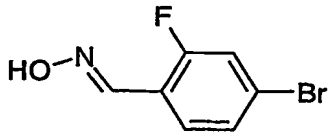
A mixture of (5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (516 mg, 1.33 mmol), 5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-[2-fluoro-4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole (758 mg, 1.6 mmol) and copper (I) iodide (104 mg, 0.53 mmol) in dry 1-methyl-2-pyrrolidinone (2 mL) was degassed and maintained under an atmosphere of argon. The mixture was treated with *tetrakis*(triphenylphosphine)palladium(0) (140 mg, 0.13 mmol) and the reaction mixture was stirred for 16 hours at 90°C. The reaction mixture was cooled and partitioned between aqueous potassium fluoride solution (100 mL , 2M) and ethyl acetate (100 mL). The ethyl acetate layer was separated, dried over magnesium sulphate, filtered, and the product was concentrated *in vacuo* onto Isolute HM-N (5 mL). The product was purified by chromatography (SiO_2 20g bond elut: elution gradient 0% to 5% methanol:dichloromethane) to give the title compound (499 mg 66%).

MS (ESP+): $(M+H)^+$ 617.17 for $C_{28}H_{33}F_2N_5O_4Si$

NMR (DMSO-d_6) δ: 0.06 (s, 3H); 0.08 (s, 3H); 0.85 (s, 9H); 3.28 (m, 1H); 3.50 (dd, 1H); 3.75 (m, 2H); 3.98 (dd, 1H); 4.32 (t, 1H); 4.82 (m, 1H); 4.88 (d, 2H); 5.20 (m, 1H); 7.42 (m, 1H); 7.49 to 7.72 (m, 4H); 7.79 to 7.85 (m, 2H); 8.21 (s, 1H).

The intermediates for these compounds were prepared as follows :-

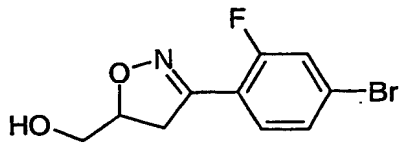
4-Bromo-2-fluorobenzaldehyde oxime



The title compound was prepared from 4-bromo-2-fluorobenzaldehyde by essentially the same method as that described in Example 1 for 4-bromo-2-methoxybenzaldehyde oxime

NMR (DMSO-d_6) δ: 3.29 (s, 1H); 7.46 (d, 1H); 7.65 (d, 1H); 7.70 (t, 1H); 8.20 (s, 1H).

[3-(4-Bromo-2-fluorophenyl)-4,5-dihydroisoxazol-5-yl]methanol

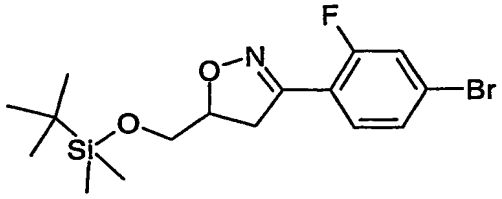


The title compound was prepared from 4-bromo-2-fluorobenzaldehyde oxime by essentially the same method as that described in Example 1 for [3-(4-bromo-2-methoxyphenyl)-4,5-dihydroisoxazol-5-yl]methanol.

MS (ESP+): $(M+H)^+$ 274 & 276 for $C_{10}H_9BrFNO_2$

NMR (DMSO-d_6) δ: 3.25 (dd, 1H); 3.44 (dd, 1H); 3.50 to 3.61 (m, 2H); 4.74 (m, 1H); 5.01 (s, 1H); 7.52 (dd, 1H); 7.68 to 7.73 (m, 2H).

3-(4-Bromo-2-fluorophenyl)-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole

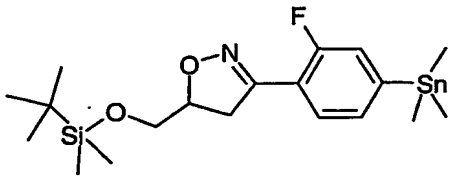


A stirred solution of [3-(4-bromo-2-fluorophenyl)-4,5-dihydroisoxazol-5-yl]methanol (1.388 g, 4.9 mmol) in a mixture of triethylamine (0.82 mL , 5.9 mmol) and dichloromethane (30 mL) was treated at 0°C dropwise during 30 minutes with a solution of solution of *tert*-butyldimethylsilylchloride (1M; 5.4 mL) in dichloromethane and then with 4-dimethylaminopyridine (0.06 g, 0.5 mmol). The reaction mixture was stirred overnight at room temperature and then washed with water (100 mL). The dichloromethane layer was dried over magnesium sulfate and filtered and the product was concentrated *in vacuo* onto Isolute HM-N (10 mL). The product was purified by chromatography [SiO_2 50g bond elut; elution gradient 0% to 25% ethyl acetate:hexanes] to give the title compound (1.286 g 68%) as a solid.

MS (ESP+): $(M+H)^+$ 387.90 & 389.9 for $C_{16}H_{23}BrFNO_2Si$

NMR (DMSO-d_6) δ: 0.05 (s, 3H); 0.06 (s, 3H); 0.83 (s, 9H); 3.25 (dd, 1H); 3.45 (dd, 1H); 3.66 to 3.80 (m, 2H); 4.79 (m, 1H); 7.52 (dd, 1H); 7.66 to 7.74 (m, 2H).

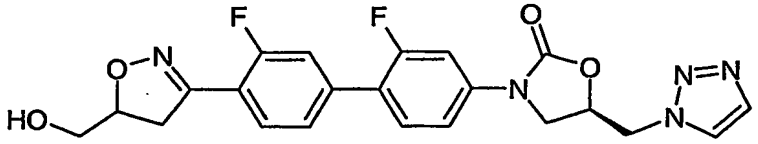
5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-[2-fluoro-4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole



A stirred solution of 3-(4-bromo-2-fluorophenyl)-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole (1.286 g, 3.31 mmol) in dry 1,4-dioxane (20 mL) was degassed and maintained under an atmosphere of argon. The mixture was treated with hexamethylditin (1.2 g, 3.64 mmol) and then with *bis*(triphenylphosphine)palladium(II) chloride (0.116 g, 0.17 mmol) and stirred at 90°C for 90 minutes under an atmosphere of argon. The reaction mixture was cooled and solvent was removed *in vacuo* to give a crude product that was re-dissolved in ethyl acetate (100 mL), absorbed onto silica-gel (5 mL) and then purified by chromatography [SiO_2 50g bond elut: elution gradient 0% to 12.5% ethyl acetate:hexanes] to give the title compound (0.758 g 48%) as a solid.

NMR (DMSO-d_6) δ: 0.05 (s, 3H); 0.07 (s, 3H); 0.32 (t, 9H); 0.84 (s, 9H); 3.23 (dd, 1H); 3.45 (dd, 1H); 3.73 (m, 2H); 4.77 (m, 1H); 7.37 to 7.43 (m, 2H); 7.67 (t, 1H).

Example 4. (5*R*)-3-{2,3'-Difluoro-4'-[5-(hydroxymethyl)-4,5-dihydroisoxazol-3-yl]-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



A stirred solution of (5*R*)-3-{4'-[5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2,3'-difluoro-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (496 mg, 0.87 mmol) in dichloromethane (10 mL) was treated at room temperature with a solution of tetrabutylammonium fluoride in tetrahydrofuran (1M; 0.96 mL , 0.96 mmol) for 180 minutes. The product was then fractionated by chromatography [SiO_2 20g bond elut; elution gradient 0% to 6% methanol:dichloromethane] to give a crude product solution that was evaporated, treated with water (100 mL), and isolated by filtration to give the title compound (190 mg 40%).

MS (ESP+): $(M+H)^+$ 455.98 for $C_{22}H_{19}F_2N_5O_4$

NMR (DMSO-d_6) δ: 3.27 (m, 1H); 3.49 (dd, 1H); 3.55 (q, 2H); 3.98 (dd, 1H); 4.32 (t, 1H); 4.76 (m, 1H); 4.88 (d, 2H); 5.04 (t, 1H); 5.20 (m, 1H); 7.42 (dd, 1H); 7.49 to 7.61 (m, 3H); 7.69 (t, 1H); 7.79 (d, 1H); 7.84 (t, 1H); 8.21 (d, 1H).

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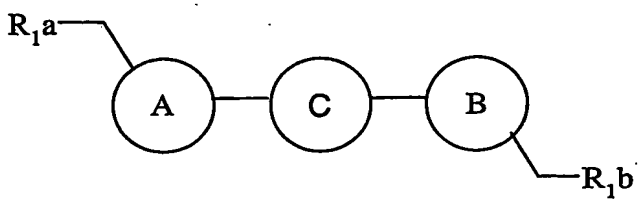
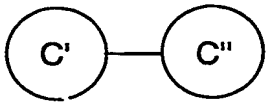
Claims

1. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

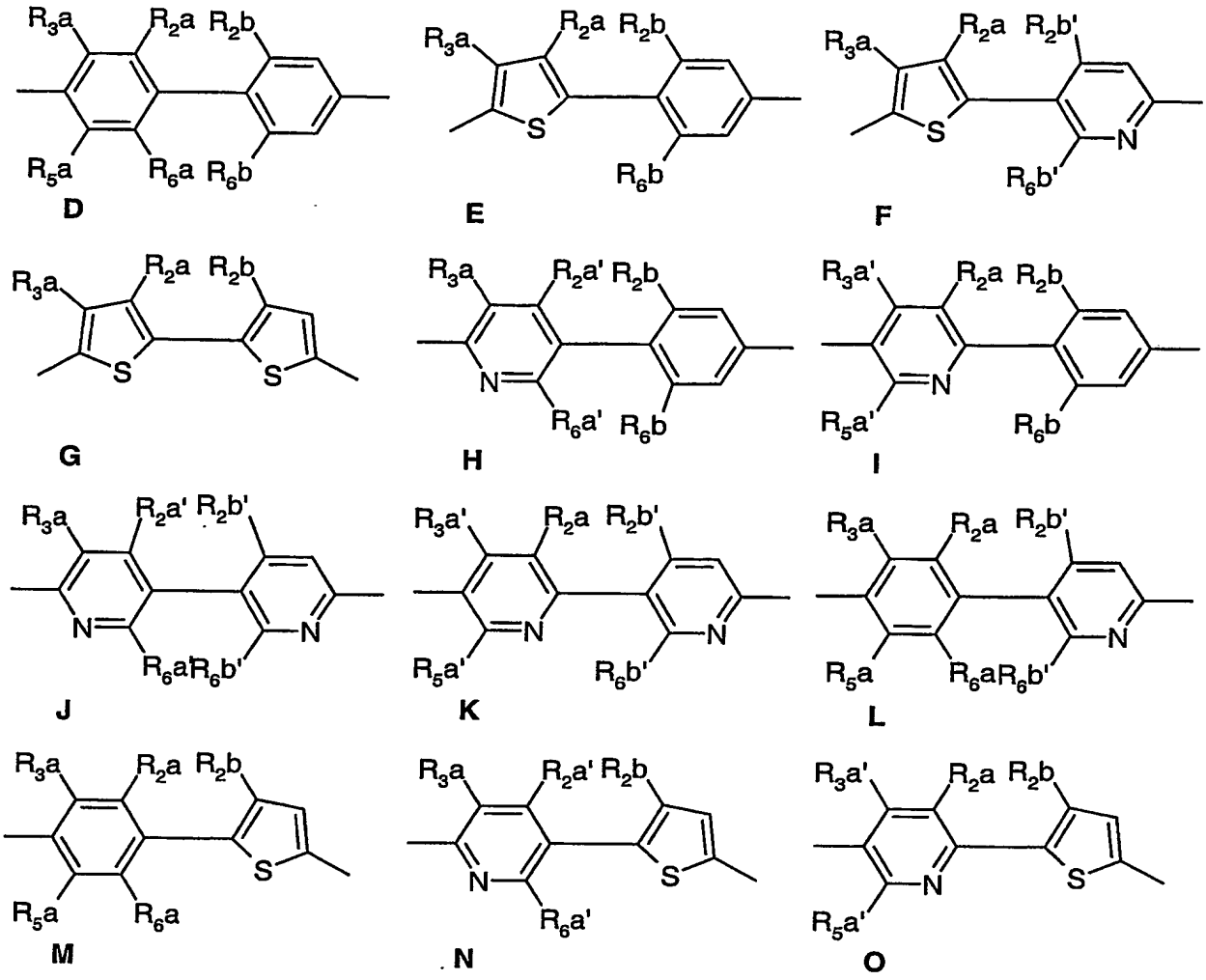


(I)

wherein in (I) C is a biaryl group C'-C''



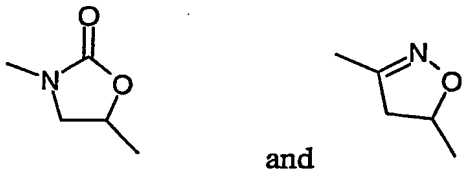
where C' and C'' are independently aryl or heteroaryl rings such that the group C is represented by any one of the groups D to O below:



wherein the groups D to O are attached to rings A and B orientation [(A-C') and (C''-B)] shown and

wherein A and B are independently selected from

i) ii)



and

wherein i) and/or ii) are linked as shown in (I) via the 3-position to group C and substituted in the 5-position as shown in (I) by $-CH_2-R_1a$ and $-CH_2-R_1b$;

R_2b and R_6b are independently selected from H, F, Cl, OMe, Me, Et and CF_3;

R_2b' and R_6b' are independently selected from H, OMe, Me, Et and CF_3;

R_2a and R_6a are independently selected from H, Br; F, Cl, OMe, SMe; Me, Et and CF_3;

R_2a' and R_6a' are independently selected from H, OMe, SMe; Me, Et and CF_3;

R_3a and R_5a are independently selected from H, (1-4C)alkyl, Br, F, Cl, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2), amino, (1-4C)alkylcarbonylamino, nitro, cyano, -CHO, -CO(1-4C) alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

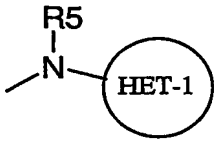
R_3a', R_5a' are independently selected from H, (1-4C)alkyl, OH, (1-4C)alkoxy, (1-4C)alkylthio, amino, (1-4C)alkylcarbonylamino, nitro, cyano, -CHO, -CO(1-4C)alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

wherein any (1-4C)alkyl group may be optionally substituted with F, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2) or cyano;

wherein at least one of R_2a, R_6a R_2a', R_6a' R_3a, R_5a, R_3a', R_5a' is not H;

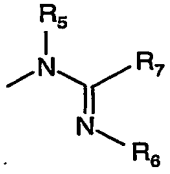
wherein when ring C' is a pyridine ring (ie when group C is group H, I, J, K, N or O) the ring nitrogen may optionally be oxidised to an N-oxide;

R_1a and R_1b are independently selected from hydroxy, -OSi(tri-(1-6C)alkyl) (wherein the 3 (1-6C)alkyl groups are independently selected from all possible (1-6C)alkyl groups), $-NR_5C(=W)R_4$, $-OC(=O)R_4$,



a) , b)

and c)



wherein W is O or S;

R_4 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, (1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)$p(3-6C)cycloalkyl or $-(CH_2)$p(3-6C)cycloalkenyl wherein p is 0, 1 or 2; and wherein at each occurrence, alkyl, alkenyl, cycloalkyl cycloalkenyl in substituents in R_4 is optionally substituted with one, two, three or more F, Cl or CN;

R_5 is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl), $-CO_2R_8$, $-C(=O)R_8$, $-C(=O)SR_8$, $-C(=S)R_8$, $P(O)(OR_9)(OR_{10})$ and $-SO_2R_{11}$, wherein R_8, R_9, R_{10} and R_{11} are as defined hereinbelow;

HET-1 is selected from HET-1A and HET-1B wherein:

HET-1A is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms

independently selected from N, O and S; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one or two substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-1B is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one, two or three substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2 is selected from HET-2A and HET-2B wherein

HET- 2A is an N-linked 5-membered, fully or partially unsaturated heterocyclic ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom, other than a C atom adjacent to the linking N atom, by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by a substituent selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2B is an N-linked 6-membered di-hydro-heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom, other than a C atom adjacent to the linking N atom, by oxo or thioxo and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by one or two substituents independently selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

RT is selected from a substituent from the group:

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro; or

(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino, and (2-4C)alkenylamino;

or RT is selected from the group

(RTb1) (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or

(RTb2) (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl,and (3-6C)cycloalkenyl;

or RT is selected from the group

(RTc) a fully saturated 4-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or carbon atom;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), (RTb1) or (RTb2), or (RTc) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;

R_6 is cyano, -COR_{12}, -$COOR_{12}$, -$CONHR_{12}$, -$CON(R_{12})(R_{13})$, -SO_2R_{12}, -SO_2NHR_{12}, -$SO_2N(R_{12})(R_{13})$ or NO_2, wherein R_{12} and R_{13} are as defined hereinbelow;

R_7 is hydrogen, amino, (1-8C)alkyl, -NHR_{12}, -$N(R_{12})(R_{13})$, -OR_{12} or -SR_{12}, (2-4C)alkenyl, (1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, -(CH_2)p(3-6C)cycloalkyl or -(CH_2)p(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_8 is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy, cyano, up to 3 halogen atoms and -$NR_{15}R_{16}$ (wherein R_{15} and R_{16} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{15})(R_{16})$ group, R_{15} and R_{16} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring);

R_9 and R_{10} are independently selected from hydrogen and (1-4C)alkyl;

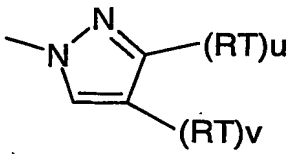
R_{11} is (1-4C)alkyl or phenyl;

R_{12} and R_{13} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{12})(R_{13})$ group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring which ring may be optionally substituted by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl.

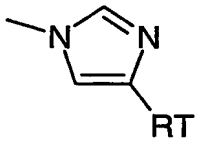
2. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 1 wherein group C is selected from groups D, E, H and I.

3. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 1 or claim 2, wherein R_1a and R_1b are independently selected from -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl , -NHCS(1-4C)alkyl, -N(R_5)-HET-1 and HET-2.

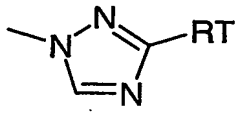
4. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 1, claim 2 or claim 3, wherein HET-2A is selected from the structures (Za) to (Zf) below:



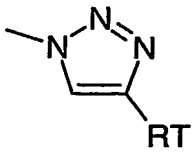
(Za)



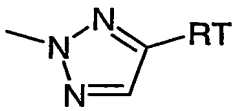
(Zb)



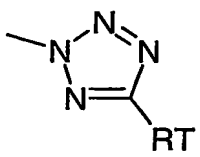
(Zc)



(Zd)



(Ze)



(Zf)

wherein u and v are independently 0 or 1.

5. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 4 wherein RT is selected from

(a) hydrogen;

(b) halogen;

(c) cyano;

(d) (1-4C)alkyl;

(e) monosubstituted (1-4C)alkyl;

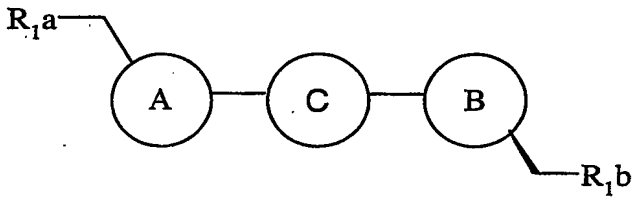
(f) disubstituted (1-4C)alkyl, and

trisubstituted (1-4C)alkyl.

6. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in any preceding claim wherein at least one of A and B is an oxazolidinone.

7. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in any preceding claim wherein both A and B are oxazolidinones.

8. A compound of the formula (IA) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in any preceding claim.



(IA)

9. A pro-drug of a compound as claimed in any one of the previous claims.

10. A method for producing an antibacterial effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

11. A compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament.

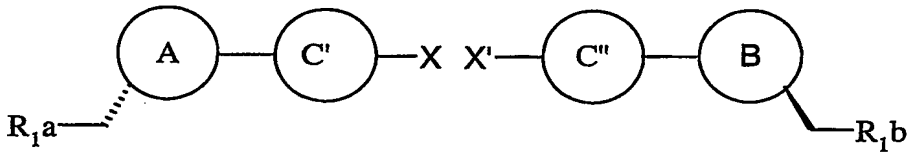
12. The use of a compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal.

13. A pharmaceutical composition which comprises a compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

14. A process for the preparation of a compound of formula (I) as claimed in claim 1 or pharmaceutically acceptable salts or in-vivo hydrolysable esters thereof, which process comprises one of processes **(a)** to **(h)**:

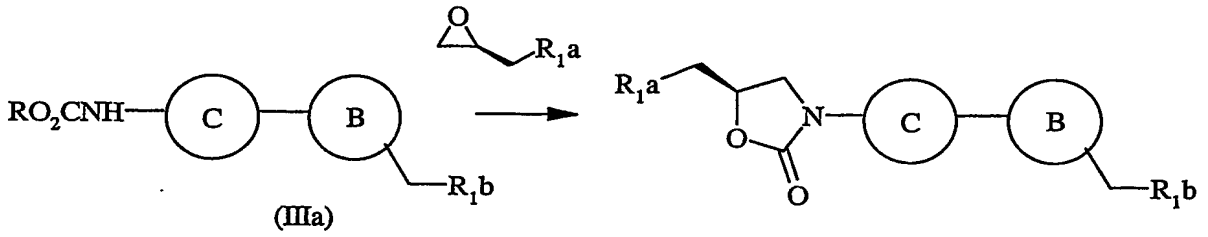
(a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry;

(b) by reaction of a molecule of a compound of formula (IIa) with a molecules of a compound of formula (IIb), wherein X and X' are leaving groups useful in palladium coupling and are chosen such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds.

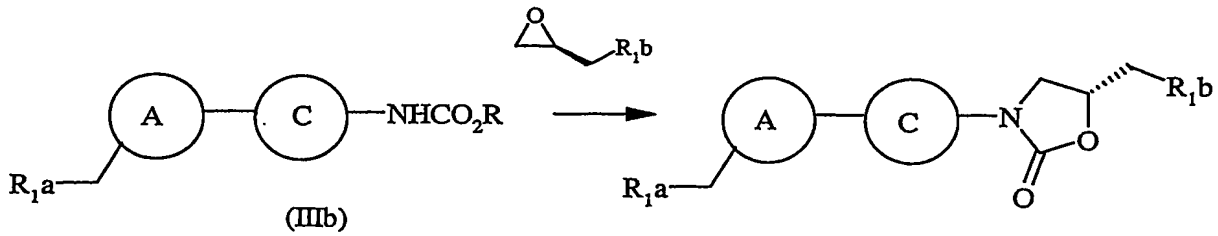


(IIa) **(IIb)**

c) by reaction of a (hetero)biaryl derivative (IIIa) or (IIIb) carbamate with an appropriately substituted oxirane to form an oxazolidinone ring at the undeveloped aryl position.



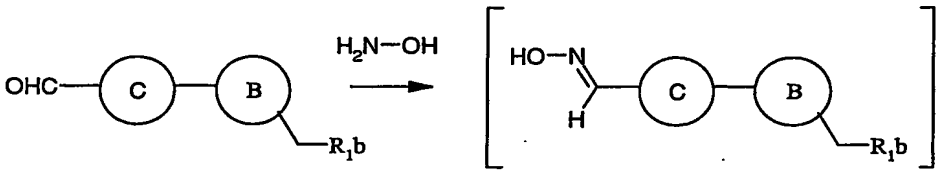
(IIIa)



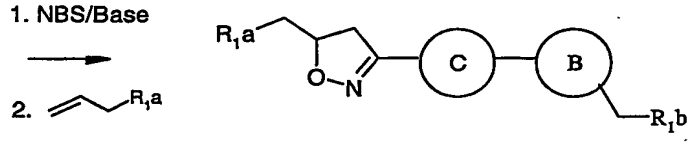
(IIIb)

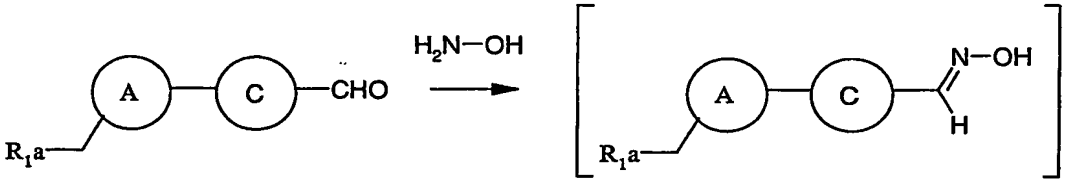
or by variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-CH_2CH(O-optionally protected)CH_2R_1a or X-CH_2CH(O-optionally protected)CH_2R_1b where X is a displaceable group

d) by reaction of a (hetero)biaryl derivative (IVa) or (IVb) to form an isoxazoline ring at the undeveloped aryl position.

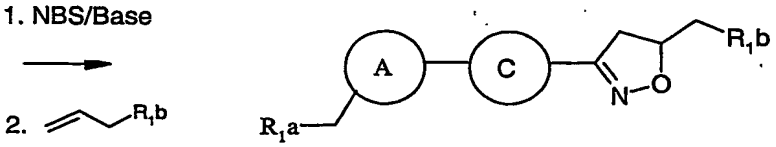


(IVa) (IVa')

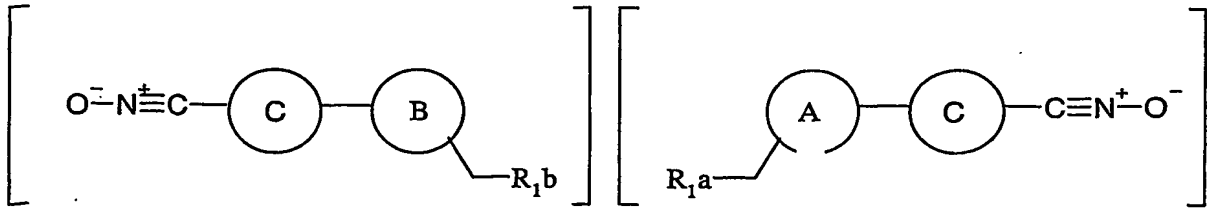




(IVb) (IVb')



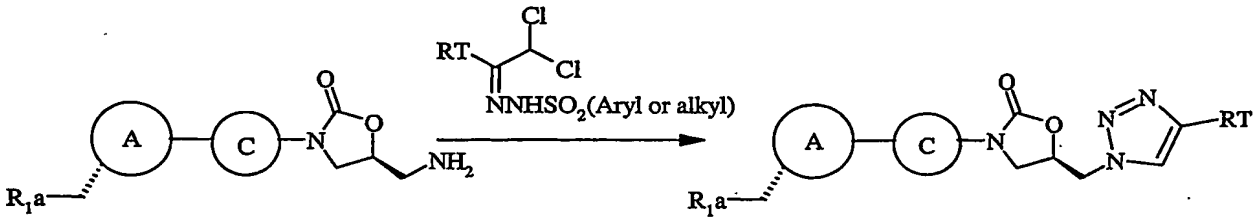
or by variations on this process in which the reactive intermediate (a nitrile oxide IVa'' or IVb'') is obtained other than by oxidation of an oxime (IVa') or (IVb') .



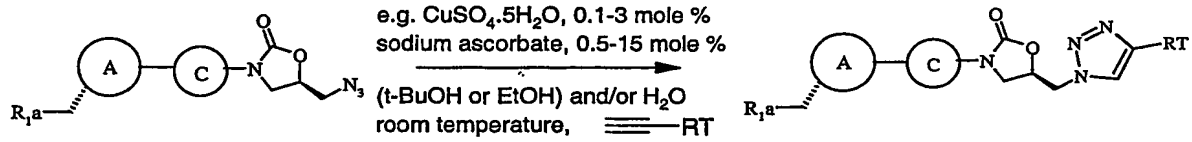
(IVa") (IVb")

(e) for HET as optionally substituted 1,2,3-triazoles, compounds of the formula (I) may be made by cycloaddition via the azide (wherein e.g. Y in (II) is azide) to acetylenes, or to acetylene equivalents such as optionally substituted cylcohexa-1,4-dienes or optionally substituted ethylenes bearing eliminatable substituents such as arylsulfonyl;

(f) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may be made by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones, for instance



(g) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with terminal alkynes using Cu(I) catalysis in e.g. aqueous alcoholic solution at ambient temperatures to give 4-substituted 1,2,3-triazoles ; for instance



(h) for HET as 4-halogenated 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides at a temperature between 0 °C and 100 °C either neat or in an inert diluent such as chlorobenzene, chloroform or dioxan; for instance.